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Docket No.: SAEG108.001APC

March 17, 2006

Please Direct All Correspondence to Customer Number **20995**

TRANSMITTAL LETTER--APPEAL BRIEF

Applicant	:	Shinichiro Morita et al.
App. No	:	10/070938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	David M. Naff
Art Unit	:	1651

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

March 17, 2006
(Date)

Daniel E. Altman, Reg. No. 34,115

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing are the following enclosures:

(X) Appeal Brief in 17 pages.

(X) Evidence Appendix (tabs 1-10)

(X) Return prepaid postcard.

FEE CALCULATION				
FEE TYPE		**FEE CODE**	**CALCULATION**	**TOTAL**
Appeal Brief	*41.20(b)(2)*	1402 ($500)		$500
3 Month Extension	*1.17(a)(3)*	1253 ($1,020)		$1,020
			TOTAL FEE DUE	$1520

(X) A 3-month extension of time is hereby requested by payment of the fee indicated above.

(X) A check in the amount of $1520 is enclosed. Please charge additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Dated: March 17, 2006

Daniel E. Altman
Registration No. 34,115
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Please Direct All Correspondence to Customer Number **20995**

APPEAL BRIEF

Applicant	:	Shinichiro Morita et al.
App. No	:	10/070,938
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Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the Notice of Appeal filed October 17, 2005, Applicant submits this Appeal Brief.

TABLE OF CONTENTS

I. REAL PARTIES IN INTEREST

Pursuant to 37 C.F.R. § 1.192, Appellants hereby notify the Board of Patent Appeals and Interferences that the real parties in interest are the assignees of this application: Gunze, Ltd., 1, Zeze, Aono-cho, Ayabe-shi, Kyoto 623-0051, Japan: and Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

III. STATUS OF CLAIMS

The above-identified application was filed with 11 claims. Claims 1-11 were rejected by the Examiner in an Office Action mailed September 8, 2004. Subsequently, Claims 12-14 were added. Claims 1-14 were finally rejected in an Office Action mailed May 17, 2005. Subsequent to that Office Action, Claims 1-6 and 12-14 were cancelled and Claims 15-19 were added. The new claims were entered for purposes of appeal by the Examiner in an Advisory Action mailed October 12, 2005, in which the Examiner indicated that Claims 7-11 and 15-19 remained rejected. Accordingly, Claims 7-11 and 15-19 are the subject of this appeal. The claims are attached hereto as Section VIII.

IV. STATUS OF AMENDMENTS

In the advisory action mailed October 12, 2005, the Examiner indicated that the amendments filed subsequent to the final rejection of the claims would be entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to Appellant's discovery of a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue. The matrix includes a sponge made of a bioabsorbable material that is reinforced with a bioabsorbable material. The sponge allows cells seeded thereon to adhere firmly thereto, enables the matrix to be absorbed *in vivo* once the blood vessel is regenerated, and allows the matrix to maintain sufficient strength to permit blood flow until the blood vessel is regenerated *in vivo*. See, e.g., specification at p. 3, lines 9-20.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner has rejected Claims 7-11 and 15-19 under 35 U.S.C. § 103(a) as being unpatentable over Naughton, et al., United States Patent No. 5,863,531, in view of Vyakarnam, et al., United States Patent No. 6,534,084, taken with Hinsch, et al., European Patent No. EP 0 274 898, and Morita, Japanese Patent No. 3-23864.

VII. ARGUMENT

The Examiner has maintained his rejection of Claims 7-11 and 15-19 under 35 U.S.C. § 103(a) as obvious over a combination of Naughton and Vyakarnam with Hinsch and Morita. The Examiner maintained the rejection based on allegations that

(A) the cited combination teaches or suggests all the claim limitations, including that the "matrix surface is completely covered with the cells," which the Examiner implies is inherent in the prior art disclosures;

(B) one of skill in the art would have a motivation to combine the references, despite the fact that Hinsch and Morita do not relate to tissue culture, and neither Naughton nor Vyakarnam disclose or suggest that a matrix to be used for culturing cardiovascular tissue should be reinforced using a bioabsorbable material; and

(C) Applicant's disclosure of the unexpected effect that a cardiovascular graft produced according to the teachings of the prior art failed rapidly whereas one produced in accordance with the claimed invention was successful is unpersuasive, because "it would have been obvious to reinforce the vessel before implanting."

Each of these allegations is addressed below.

A. The Examiner has Failed to Establish a *Prima Facie* Case of Obviousness, Because Certain Claim Limitations Are Not Found in the Cited Combination of References

In order to establish a *prima facie* case of obviousness, the Examiner is required to demonstrate that all of the limitations of the claims are present in or suggested by the prior art. See M.P.E.P. § 2143.03. The Examiner has failed to demonstrate that certain limitations of the pending claims are present in or suggested by the prior art.

Claim 7, the only pending independent claim, contains the limitation of "culturing the cells until the matrix surface is completely covered with the cells," which is accomplished before the regenerated tissue is implanted. In the Advisory Action mailed October 12, 2005, the Examiner states that "Naughton et al. disclose seeding a matrix with cells and producing in vitro tissue such as a tubular tissue structure, and implanting the tissue structure. In producing such tissue structure, the matrix will be completely covered with cells or otherwise the structure not be [sic] formed." In other words, the Examiner relies on a conclusory assertion that the production of in vitro tissue on the matrix necessarily involves the complete covering of the matrix with cells. The Examiner offers no support for this other than his linkage between the complete covering of the matrix with the cells and the formation of the structure. However, the Naughton patent that the Examiner relies on for support itself does not indicate that the production of a tissue structure necessarily requires that the matrix surface be "completely covered." As Naughton describes the process of forming a tissue:

> During growth in vitro the stromal cells deposit their extracellular matrix proteins onto the framework, thus forming a living stromal tissue; i.e., the stromal cells and connective tissue proteins naturally secreted by the stromal cells attach to and substantially envelope the framework composed of a biocompatible non-living material formed into a three-dimensional structure having interstitial spaces bridged by the stromal cells. (Emphasis added).

Naughton at col. 4, lines 30-38. This appears to be the only direct description in Naughton of the extent to which the framework is covered before implantation.

During patent examination, claims must be "given their broadest reasonable interpretation consistent with the specification." In re Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000); M.P.E.P. § 2111. A relevant definition of "complete," as an adjective, is "finished; ended; concluded;" and as a verb, "to bring to an end; finish." Webster's Encyclopedic Dictionary of the English Language 301 (1989). The broadest reasonable interpretation of "completely covered" is that the term means the matrix is covered in its entirety. It would be unreasonable to interpret the claim to read on a method step in which the matrix was less than completely covered, given the plain meaning of "completely."

Yet Naughton's description of the framework as "substantially enveloped" shows that the Examiner has in effect given the "completely covered" limitation just such an unreasonably broad interpretation. A relevant definition of "substantial," as an adjective, is "of ample or considerable amount, quantity, size, etc." Webster's Encyclopedic Dictionary of the English Language 1418 (1989). A framework that is covered only to a "considerable amount" is not, however, "completely" covered. Naughton's description therefore excludes the possibility that the framework is completely covered. To use an analogy, if a job has been "substantially" finished, it is clear that work remains to be done and the job is not yet complete. In the same way, Naughton's description of the framework as "substantially" enveloped (rather than "at least substantially enveloped" or "enveloped or substantially enveloped") indicates that the process of envelopment is not yet complete. Neither in this passage nor elsewhere in the Naughton disclosure does it disclose that the cells must "completely cover" the matrix before the implantation of the in vitro tissue.

Neither does Vyakarnam, U.S. Patent No. 6,534,084, disclose or suggest that the cells must "completely cover" the matrix before implantation, as presently claimed. At most, Vyakarnam discloses that the foam employed as the matrix would be "implanted into the donor patient once the cells have invaded the microstructure of the device." Vyakarnam at col. 19, lines 14-15. Vyakarnam does not teach or suggest, however, that this invasion of the microstructure of the device must result in complete coverage of the foam by the seeded cells before implantation. Furthermore, Vyakarnam's working in vivo example did not involve tissue engineering at all: the unseeded foam matrix was implanted into a swine dermal wound, and cellular invasion of the implant was assessed after eight days. Vyakarnam thus does not disclose that the seeded cells must "completely cover" the matrix before implantation.

Furthermore, the Examiner has conceded that "Hinsch et al. and the Japanese patent may not seed the foam with cells before implanting." Advisory Action mailed October 12, 2005 at 2. Because no seeding of cells takes place before implantation, these references cannot disclose complete coverage of the matrix surface with the cultured cells before implantation in the patient.

Because the Examiner has not established that any of the cited references either teach or suggest completely covering the matrix surface with seeded cells before implanting the matrix in a patient, he has not established a *prima facie* case of obviousness. Accordingly, the rejection of the pending claims under 35 U.S.C. § 103(a) is legally deficient and should be reversed on this ground.

B. There is No Suggestion or Motivation in the Cited References or in the Knowledge Generally Available to One of Ordinary Skill to Combine Reference Teachings

1. The Examiner Has Identified No Motivation, Teaching, or Suggestion to Combine Bioabsorbable Reinforcements With Tubular Foam Structures

The Examiner relies on an unsupported assertion that the combination of the biodegradable reinforcements of Hinsch and Morita with the tubular foam of Naughton and Vyakarnam would have been obvious to one of skill in the art. "It would have been . . . obvious to reinforce the foam with fibers as suggested by Hinsch et al. and the Japanese patent using fibers to reinforce a foam implant." Office Action mailed May 17, 2005 at 4. He offers no other ground for concluding that this combination would have been obvious to one of ordinary skill in the art.

Because the Examiner has relied on a conclusory assertion of obviousness, he has failed to meet his burden of "showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988) ("The PTO has the burden under section 103 to establish a *prima facie* case of obviousness."). Unsupported assertions that the combination would have been obvious cannot substitute for the required objective teaching that would suggest the combination. "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." In re Lee, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002) (vacating a conclusion of obviousness based on the Examiner's "conclusory statements" that did not "adequately address the issue of motivation to combine").

2. The Examiner's Stated Motivation to Combine is Based on A Misunderstanding of the Cited References

The Examiner goes on to cite the disclosure in Vyakarnam of bioabsorbable reinforcement of a foam matrix used for engineering cartilaginous tissue to be attached to bone: "The foam [of Vyakarnam] can be reinforced with fibers (col. 6, line 40)." Office Action mailed May 17, 2005 at 3. He implies that one of skill in the art would have understood from this that bioabsorbable reinforcements such as those in Hinsch and Morita should have been used in cardiovascular tissue, as in the pending claims:

> [S]ince the foam of Vyakarnam et al. which is used for tissue engineering can be reinforced with fibers, it would have been apparent that reinforcement is important irrespective of whether tissue is produced on the foam or sponge before implanting. Even after tissue is engineered on the foam or sponge it is implanted and reinforcement would have expected to be important for the same type of reasons as when tissue is not produced on the foam or sponge before implanting.

Id. at 5.

Here, the Examiner builds on his unsupported assertion of obviousness by citing only that teaching of Vyakarnam that he believes supports his conclusion. This in itself is impermissible: it is clear that in an obviousness context "the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination." See M.P.E.P. § 2141 (emphasis added). The Examiner has improperly discounted not only other aspects of the Vyakarnam reference, but also passages in the Hinsch and Morita references that Applicant cited to the Examiner during prosecution, that indicate one of skill in the art would not have been motivated to make the combination. As discussed in greater detail below, Hinsch indicates that biodegradable reinforcement is necessary because of the open-cell structure of the unseeded implant, while Morita suggests that biodegradable reinforcement is only necessary until the tissue is regenerated on the implant in vivo. Also fatal to the Examiner's case is the fact that he has misunderstood the implications of the single passage from Vyakarnam to which he refers. Properly understood, that passage is at best irrelevant to the question of whether one of skill in

the art would have been motivated to use a bioabsorbable reinforcement in cardiovascular tissue grafts produced in vitro.

a. <u>The Cited Section of Vyakarnam Neither Relates to Tissue Engineering Nor to Tissue Requiring Elasticity</u>

As quoted above, the Examiner points to the disclosure in Vyakarnam of a reinforced foam matrix for use in tissue engineering. However, in the passage cited, Vyakarnam discloses the use of a reinforcement made of a bioabsorbable material in the context of tissue to be used at the interface between cartilage and bone:

> For articular cartilage, it is currently preferred that the <u>stiffness</u> (modulus) of the upper and lower porous layers at the time of implantation be at least as stiff, as the corresponding adjacent tissue. In such a case the porous layers will be able to support the environmental loading and thereby protect the invading cells until they have differentiated and consolidated into tissue that is capable of sustaining load . . . . Finally, at the bottom of this structure there is a need for larger pores (about 150 μm to about 300 μm) with higher <u>stiffness</u> to be structurally compatible with cancellous bone. The foam in this section could be reinforced with ceramic particles or fibers made up of calcium phosphates and the like.

Vyakarnam at col. 6, lines 16-41 (emphasis added).

This disclosure appears not to relate to tissue engineering techniques. Vyakarnam is concerned in this section with the "stiffness... at the time of implantation" and that the layers of the matrix when implanted "be able to support the environmental loading and thereby protect the invading cells <u>until they have differentiated and consolidated into tissue</u> that is capable of sustaining load." <u>Id.</u> (emphasis added) Therefore the Examiner's assumption that this disclosure relates to tissue engineering methods such as those claimed in the present application is unwarranted.

Even if the disclosure were applicable to tissue engineering techniques, however, the text cited above reveals that the need for reinforcing bioabsorbable fibers is driven by the need for <u>stiffness</u> in the implant at the cartilage-bone interface. The Examiner justified his assumption that bioabsorbable reinforcement taught to be important in cartilaginous tissue would also be important in cardiovascular tissue by noting that "cardiovascular tissue can contain cartilaginous

tissue." Advisory Action at 2. However, this does not establish that one of skill in the art would understand that the use of bioabsorbable reinforcements in a matrix to be employed in generating cartilaginous tissue that is attached to bone (and that is specifically taught to require stiffness) should be extended to the use of bioabsorbable reinforcements in cardiovascular tissue as in the pending claims. In fact, as discussed in more detail in section C below, it is clear that cardiovascular tissue and its associated connective tissue require elasticity, not stiffness.

Furthermore, although Vyakarnam specifically describes possible tissue scaffoldings for use in skin and vascular repair, the reference does not disclose the use of bioabsorbable reinforcements in such applications. By inference, Vyakarnam does not suggest to one of skill in the art that the use of bioabsorbable reinforcements is preferable where higher stiffness is not required, such as in vascular repair.

b. Hinsch and Morita Do Not Contemplate Ex Vivo Tissue Engineering and Use Bioabsorbable Reinforcements to Support the Grafts Until Tissue Forms In Vivo

As the Examiner has conceded, neither Hinsch nor Morita teach ex vivo seeding of cells onto the open-cell foam or sponge that was to be implanted. It is therefore not surprising that they should have been concerned with strengthening the porous implant before subjecting it to the stresses present in vivo. Hinsch, for example, described an object of his invention as "to propose implants which, despite the adequately open-cell structure to permit the growing in of cells and blood vessels, have an adequate strength and in particular tensile strength." Hinsch at p. 2, lines 51-53. Furthermore, Morita suggests that this reinforcement is not necessary when fully regenerated tissue is present. Specifically, the implant disclosed in Morita is said to "maintain[] its strength and shape over a long period of time until the regeneration of the tissue." Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). By implication, regenerated tissue would not require the bioabsorbable reinforcement disclosed in Hinsch and Morita. Therefore, in contrast to the Examiner's understanding that "reinforcement would have expected to be important for the same type of reasons as when tissue is not produced on the foam or sponge before implanting," Office Action mailed May 17, 2005 at 5, these references suggest that reinforcement would not be required when tissue is regenerated before implantation.

In short, one of skill in the art, reading these references before the claimed invention was made, would have understood them to teach that replacement tissues grown on the disclosed matrices or foams without a bioabsorbable reinforcement have sufficient strength to be implanted in the body as prosthetic cardiovascular tissue once the tissue culture is complete, such that the inclusion of a bioabsorbable reinforcement was not required. For this reason, there is no suggestion or motivation in the prior art to combine the cited references, and the Examiner's rejection of the pending claims as obvious under 35 U.S.C. § 103(a) is thus legally deficient and should be reversed.

C. <u>The Cited References Teach Away From the Cited Combination</u>

Furthermore, the Examiner has improperly discounted aspects of the cited references that, in combination, teach away from the combination of the references.

Specifically, Naughton discloses foam structures that may be used in regenerating vasculature in vitro. However, Naughton does not teach the use of bioabsorbable fibrous reinforcing materials such as those of the present application. In fact, Naughton specifically criticizes the use in the prior art of artificial materials to provide "the strength and elasticity required of blood vessels in vivo," and notes that the criticized prior art technique resulted in a construction that "completely lacked elastin." Naughton '531 at col. 4, lines 2-6. The presence of elastin "gives arteries the ability to stretch with every contraction of the heart." Naughton '531 at col. 24, lines 48-50. Naughton suggests that when natural components such as elastin are present in tubular biological replacement tissues grown on an unreinforced matrix, they may be used as replacement tissues in the body:

> The different biological structures described below have several features in common. They are all tubular structures primarily composed of layers of stromal tissue with an interior lining of epithelium (gastrointestinal and genitourinary) or endothelium (blood vessels). Their connective tissues also contain layers of smooth muscle with varying degrees of elastic fibers, both of which are especially prominent in arterial blood vessels. By including and sustaining these components in three-dimensional cultures according to the present invention, the tissues they compose can attain the special structural and functional properties they require for proper physiological functioning in vivo. They can then serve as replacements for damaged or diseased tubular tissues in a living body.

Naughton '531 at col. 22, lines 49-62. Thus there is a clear distinction between the type of connective tissue found in tubular tissue structures such as cardiovascular tissue, which Naughton describes as containing "elastic fibers," and the cartilaginous tissue found at the interface with bone, which Vyakarnam describes as requiring a high degree of stiffness. The Examiner has not taken this difference in the tissues into account in concluding that the pending claims are obvious in view of the cited combination of references.

The Examiner suggests that one of skill in the art would have been motivated to combine these references because "cardiovascular tissue contains cartilaginous tissue." Advisory Action mailed October 12, 2005 at 2. This is much too simplistic. One of skill in the art would have understood from Naughton and Vyakarnam that bioabsorbable reinforcements are required where the tissue graft requires special stiffness, such as at the cartilage-bone interface, and such reinforcements would simply not be appropriate for cardiovascular tissue, which requires elasticity. Use of the stiffening bioabsorbable reinforcements of the cited section of Vyakarnam would have impaired the elasticity required by the cardiovascular tissue, probably rendering the cardiovascular tissue graft unsuitable for its intended purpose. This would lead one of skill in the art away from the cited combination. See In re Sponnoble, 405 F.2d 578, 587 (C.C.P.A. 1969) (finding no motivation to combine references that, if combined, "would produce a seemingly inoperative device"); see also Tec Air, Inc. v. Denso Mfg. Mich. Inc., 192 F.3d 1353, 1360 (Fed. Cir. 1999) ("If when combined, the references 'would produce a seemingly inoperative device,' then they teach away from their combination." (quoting Sponnoble, 405 F.2d at 587)).

Because of this teaching away from the cited combination, there is no suggestion to combine the references. See In re Fine, 837 F.2d at 1074. Accordingly, the Examiner has not established a prima facie case of obviousness, and the Examiner's rejection of the pending claims should be reversed.

D. The Unexpected Results Demonstrated by the Applicants are Objective Evidence of Nonobviousness That the Examiner Improperly Discounted

In evaluating whether a claimed invention is obvious under Section 103, the Examiner is also required to consider whether unexpected results were obtained: "objective evidence o[f]

secondary considerations such as unexpected results ... are relevant to the issue of obviousness and must be considered in every case in which they are present." M.P.E.P. § 2141. Furthermore, all available evidence, including evidence of secondary considerations, must be considered in the course of reaching the conclusion of obviousness. In re Fine, 837 F.2d at 1073-74 ("'To reach a proper conclusion under § 103, the decisionmaker must step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention was unknown and just before it was made. In light of *all* the evidence, the decisionmaker must then determine whether ... the claimed invention as a whole would have been obvious at *that* time to *that* person.'" (quoting Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566 (Fed. Cir. 1987))).

In this case, applicants demonstrated that an engineered blood vessel graft that was not provided with a bioabsorbable reinforcement, as suggested by the prior art, failed within one week when it was grafted into the vena cava of a dog. In contrast, a cardiovascular graft that was produced using a bioabsorbable reinforcement, in accordance with the present invention, showed good patentcy on angiographic examination three months after implantation, and after six months in vivo the blood vessel had regenerated at the implantation site. See specification at pages 12-13. The Examiner dismisses these results, however: "[t]he results in Example 1 are unpersuasive, since the references suggest using fibers to reinforce tubular structures to be implanted, and it would have been obvious to reinforce the vessel before implanting. The references would not have taught reinforcement if reinforcement had not needed [sic] to provide additional strength." Office Action mailed May 17, 2005 at 6.

The Examiner appears to be placing the cart before the horse. Objective evidence of secondary considerations such as unexpected effects must be considered before determining whether an invention is obvious over the prior art. See M.P.E.P. § 2141; In re Vamco Machine & Tool, Inc., 752 F.2d 1564, 1573 (Fed. Cir. 1985) ("'[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.'" (quoting Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983))). Here, the Examiner appears to have come to the conclusion that the invention was obvious ("it would have been obvious to reinforce the vessel before implanting") and rejected the

evidence of unexpected effects on the basis of that conclusion, rather than considering the evidence before concluding that the claims were obvious.

In this case, if bioabsorbable reinforcements were in fact needed in cardiovascular grafts, the prior art would have taught or suggested that such bioabsorbable reinforcements should be used. The fact that it did not disclose or suggest the use of such bioabsorbable reinforcements, and specifically criticized the use of artificial reinforcements in cardiovascular tissue, is evidence that the use of such bioabsorbable reinforcements is not obvious.

The results obtained by the applicants demonstrate that the blood vessel grafts produced in accordance with the pending claims were unexpectedly superior to those produced by methods suggested by the prior art. This objective evidence of unexpected effects is a strong indicator that the pending claims are not obvious in view of the cited prior art. The rejection of the pending claims as obvious under 35 U.S.C. § 103(a) should be reversed on this ground.

CONCLUSION

In view of the arguments presented above, appellants submit that the pending claims are not obvious in view of the cited prior art combination and respectfully request that the Section 103(a) obviousness rejection be reversed, and that the application be allowed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Mar. 17, 2006

Daniel E. Altman
Registration No. 34,115
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Customer No. 20,995
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VIII. CLAIMS APPENDIX

1-6. (Cancelled)

7. (Previously presented) A method for regenerating cardiovascular tissue comprising:

seeding cells on a matrix comprising a sponge configured to regenerate cardiovascular tissue and made of a bioabsorbable material and a reinforcement made of a bioabsorbable material;

culturing the cells until the matrix surface is completely covered with the cells; and

embedding the matrix in vivo for regenerating cardiovascular tissue.

8. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a blood vessel.

9. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a cardiac valve.

10. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a pericardium.

11. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cells to be seeded are a mixed cell culture of two or three different kinds selected from the group consisting of endothelial cells, smooth muscle cells and fibroblasts.

12-14. (Cancelled)

15. (Previously presented) The method for regenerating cardiovascular tissue according to Claim 7, wherein the bioabsorbable material is at least one member selected from the group consisting of polyglycolic acid, polylactic acid (D form, L form, or DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymers, glycolic acid-caprolactone copolymers, lactic acid (D form, L form, DL form)-caprolactone copolymers and poly(p-dioxanone).

16. (Previously presented) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating an artery, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

17. (Previously presented) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating a vein, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polyglycolic acid.

18. (Previously presented) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating a cardiac valve or a pericardium, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

19. (Previously presented) The method for regenerating cardiovascular tissue according to Claim 7, wherein the sponge has a pore diameter of about 5 μm to about 100 μm.

IX. EVIDENCE APPENDIX

1. Specification as filed;
2. Office Action mailed September 8, 2004;
3. Response to Office Action, filed February 8, 2005;
4. Office Action mailed May 17, 2005;
5. Response to Office Action, filed September 19, 2005;
6. Advisory Action mailed October 12, 2005;
7. United States Patent No. 6,534,084;
8. United States Patent No. 5,863,531;
9. European Patent Application Publ. No. 0 274 898 A2;
10. Japanese Patent No. 03-23864 and English translation.

X. RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board in any related proceedings identified above.

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031706

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 USC 371

International Application No.: PCT/JP00/06129
International Filing Date: September 8, 2000
Priority Date Claimed: September 9, 1999
Title of Invention: MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Applicant(s) for DO/EO/US: Shinichiro Morita, Toshiharu Shin'oka and Yasuharu Imai

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. (X) This is a **FIRST** submission of items concerning a filing under 35 USC 371.

2. (X) This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).

3. (X) A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

4. (X) A copy of the International Application as filed (35 USC 371(c)(2))

   a) () is transmitted herewith (required only if not transmitted by the International Bureau).
   b) (X) has been transmitted by the International Bureau.
   c) (X) a copy of Form PCT/1B/308 is enclosed.
   d) () is not required, as the application was filed in the United States Receiving Office (RO/US).

5. (X) A translation of the International Application into English (35 USC 371(c)(2)).

6. (X) Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3))

   a) () are transmitted herewith (required only if not transmitted by the International Bureau).
   b) () have been transmitted by the International Bureau.
   c) () have not been made; however, the time limit for making such amendments has NOT expired.
   d) (X) have not been made and will not be made.

7. (X) International Application as published - face sheet only.

8. (X) International Search Report.

9. (X) PCT Request Form.

10. (X) Verification of a translation.

11. (X) International Application as published - face sheet only.

12. (X) Two (2) sheets of photo drawings.

13. (X) A return prepaid postcard.

14. (X) The following fees are submitted:

				FEES
	BASIC FEE			$890
CLAIMS	**NUMBER FILED**	**NUMBER EXTRA**	**RATE**	
Total Claims	11 - 20 =	0 ×	$18	$0
Independent Claims	1 - 3 =	0 ×	$84	$0
	TOTAL OF ABOVE CALCULATIONS		$890	
	TOTAL FEES ENCLOSED			$890

15. (X) The fee for later submission of the signed oath or declaration set forth in 37 CFR 1.492(e) will be paid upon submission of the declaration.

16. (X) A check in the amount of $890.00 to cover the above fees is enclosed.

17. (X) The Commissioner is hereby authorized to charge only those additional fees which may be required, now or in the future, to avoid abandonment of the application, or credit any overpayment to Deposit Account No. 11-1410.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Katsuhiro Arai
Reg. No. 43,315
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030602

DESCRIPTION

MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE

TECHNICAL FIELD

The present invention relates to a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue and a method for regenerating cardiovascular tissue such as an artificial blood vessel, cardiac valve, pericardium, etc.

BACKGROUND ART

In the field of artificial vessels, for instance, those made of non-bioabsorbable polymers are widely used. An artificial vessel (GORE-TEX), for example, is used most frequently in a clinical field. Such non-bioabsorbable artificial vessel is excellent in physical properties; however, because of the non-bioabsorbability, it remains in vivo as a foreign body for a long period of time after implantation. Further, when the non-bioabsorbable artificial vessel is implanted into the body of a child, another surgery for replacement is necessary since the non-bioabsorbable artificial vessel does not expand with the growth of the autogeneous blood vessel.

A tissue regeneration method employing tissue engineering techniques has recently been developed, wherein cells of autogeneous tissue are seeded and

cultured on a scaffold made of a bioabsorbable polymer so as to regenerate the autogeneous tissue. There have been published quite a few research reports of the tissue regeneration method applied to skin regeneration (M. L. Cooper, L. F. Hansbrough, R. L. Spielvogel, et al.: In vivo optimization of a living dermal substitute employing cultured human fibroblasts on a biodegradable polyglycolic acid or polyglactin mesh. Biomaterials, 12:243-248, 1991) and cartilage regeneration (C.A. Vacanti, R. Langer, et al.: Synthetic polymers seeded with chondrocytes provide a template for new cartilage formation. Plast. Reconstr. Surg., 88:753-759, 1991).

If a blood vessel can be regenerated in the same manner as described above, growth of the regenerated blood vessel is expected since it is regenerated by using autogeneous tissue and no longer necessitates the use of anti-coagulants.

An object of the present invention is to provide a matrix which allows cells to sufficiently adhere thereto, provides an optimum scaffold for cell proliferation, maintains satisfactory blood flow resistance in vivo till autogeneous tissue is regenerated, and is ultimately decomposed and absorbed in vivo.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a photograph showing a cross-sectional

view of a vascular regeneration matrix according to the present invention.

Fig. 2 is a photograph showing a plan view of a vascular regeneration matrix according to the present invention.

Fig. 3 is a photograph of the angiogram recorded at the 3rd postoperative month.

DISCLOSURE OF INVENTION

Basic requirements for the matrix for culturing cardiovascular cells to regenerate cardiovascular tissue are an ability to allow cells seeded thereon to adhere firmly thereon and a bioabsorbability which enables the matrix to be absorbed in vivo when a blood vessel is regenerated. A sponge is considered to be the optimum material to fulfill the above requirements.

In the case of using the matrix for regenerating a blood vessel, the matrix is required to maintain an enough strength to endure a blood flow for a certain period of time after implantation till the blood vessel is regenerated in vivo.

The inventors found that the above object is achieved by strengthening, with a reinforcement made of a bioabsorbable material, a sponge made of a bioabsorbable material which is an optimum scaffold for cell proliferation and excellent in cell adhesiveness.

The present invention provides a matrix for culturing cardiovascular tissue and a method for regenerating cardiovascular tissue of the following items.

Item 1. A matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material.

Item 2. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to item 1, wherein the bioabsorbable material is at least one member selected from the group consisting of polyglycolic acid, polylactic acid (D form, L form, DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymer, glycolic acid-caprolactone copolymer, lactic acid (D form, L form, DL form)-caprolactone copolymer, poly(p-dioxanone) and the like.

Item 3. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to item 1 for use in regenerating an artery, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

Item 4. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to item 1 for use in regenerating a vein, wherein the sponge comprises a lactic acid-caprolactone copolymer and the

reinforcement comprises polyglycolic acid.

Item 5. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to item 1 for use in regenerating a cardiac valve or a pericardium, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

Item 6. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to item 1, wherein the sponge has a pore diameter of about 5 μm to about 100 μm.

Item 7. A method for regenerating cardiovascular tissue comprising seeding cells on the matrix of item 1 and culturing the cells.

Item 8. The method for regenerating cardiovascular tissue according to item 7, wherein the cardiovascular tissue to be regenerated is a blood vessel.

Item 9. The method for regenerating cardiovascular tissue according to item 7, wherein the cardiovascular tissue to be regenerated is a cardiac valve.

Item 10. The method for regenerating cardiovascular tissue according to item 7, wherein the cardiovascular tissue to be regenerated is a pericardium.

Item 11. The method for regenerating cardiovascular tissue according to item 7, wherein the

cells to be seeded are a mixed cell culture of two or three different kinds selected from the group consisting of endothelial cells, smooth muscle cells and fibroblasts.

According to the invention, it is preferable that regeneration of cardiovascular tissue be conducted by seeding cells to a matrix for culturing cardiovascular cells and embedding the matrix in vivo to regenerate cardiovascular tissues in vivo.

Examples of bioabsorbable material include polyglycolic acid, polylactic acid (D form, L form, DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymer, glycolic acid-caprolactone copolymer, lactic acid (D form, L form, DL form)-caprolactone copolymer, poly(p-dioxanone) and the like.

Examples of cardiovascular tissue include blood vessels, cardiac valves, the pericardium and the like.

The matrix of the invention is obtained by strengthening a sponge made of a bioabsorbable material with a reinforcement (in the form of a fiber, nonwoven fabric or film) made of a bioabsorbable material. There is no limitation on the bio-absorbable materials to be used for the sponge and the reinforcement. In the case of preparing the matrix for regenerating a blood vessel, a sponge made of a lactic acid-caprolactone copolymer may be combined with a reinforcement made of polylactic acid when

the blood vessel is an artery, and the same sponge may be combined with a reinforcement made of polyglycolic acid when the blood vessel is a vein. Further, in the case of regenerating a cardiac valve or the pericardium, a sponge made of a lactic acid-caprolactone copolymer may be combined with a reinforcement made of polylactic acid.

The sponge has pores each having such a pore size that cells can suitably be adhered thereto to proliferate and that no blood leakage is caused when the matrix comprising the sponge is implanted as cardiovascular tissue. The pore size may typically be about 1 mm or less, preferably about 5-100 μm. The shape of the matrix may be cylindrical when the cardiovascular tissue to be regenerated is a blood vessel or may be plane when the cardiovascular tissue to be regenerated is a cardiac valve or the pericardium. In the case of regenerating a blood vessel, the length and inside diameter of the matrix may be adjusted depending on the target blood vessel. The thickness of the matrix is chosen depending on the desired period for bio-absorption or ease of suturing. The thickness may typically be about 5 mm or less, preferably from about 500 μm to about 2 mm.

For preparation of the sponge, the following alternative processes, among others, are available.

(1) Lyophilization process

A substrate polymer solution is poured in a mold, frozen, and, then lyophilized. According to the freezing temperature and polymer concentration, sponges having various pore diameters are obtained (described in Examples).

(2) Elution process

A water-soluble material is mixed with the substrate polymer solution and, after drying, the water-soluble material is washed out with rinse water. The resultant sponge has a pore diameter corresponding to the particle size of the water-soluble material used. In the present case, sucrose can be used with advantage.

The reinforcement must have a greater strength than the sponge. The reinforcement can be selected from among a fiber, nonwoven cloth, film and so on.

The reinforcement is preferably integrated with the sponge and can be located either on the interior surface, inside, or exterior surface of the sponge. However, since the interior surface of the sponge is involved in the adhesion of vascular endothelial cells, it is preferably situated inside or on the exterior surface, although the interior surface may be optionally used.

As to the cells to be seeded, substantially the same kinds of cells are used for various cardiovascular tissues in common. Thus, they are endothelial cells,

smooth muscle cells and fibroblasts, and a mixed cell culture of two or three different kinds of cells can be mentioned by way of example. Tissue construction is carried out using such mixed culture cells.

The cultural conditions for the cells to be used and the seeding method are described below.

A. Cell isolation, culture, and propagation

The vascular tissue isolated in a sterile environment is immersed in a cell culture medium and washed with phosphate-buffered saline in a clean bench. Then, on a Petri dish, the tissue is cut into pieces using a surgical knife according to the simple explant technique. Tissue pieces sized about 1-2 mm^2 are distributed uniformly on the dish and after about 20 minutes, when the tissue pieces have intimately adhered to the bottom of the dish, a culture medium is added. As the culture medium, Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10 % fetal calf serum and 1 % antibiotics solution (L-glutamine 29.2 mg/ml, penicillin G 1000 U/ml, streptomycin sulfate 10,000 µg/ml) is used. The mixed cells of endothelial cells and fibroblasts begin to migrate from the tissue pieces on the dish after 5-7 days, forming mixed-cell colonies around the explants in a further one week. After another 2-3 weeks, the mixed cells become confluent on the dish. Immediately, a passage is made

using 0.25 % trypsin and the culture in a 75 cm^2 culture flask is started. Generally when the growth in this flask has become confluent, about $2x10^6$ cells are available. Cell culture is performed under an atmosphere comprising 5 % CO_2 and 21 % O_2 and continued until $10x10^6$ cells have been obtained. While the culture medium is renewed every 4-5 days, the resultant of a preliminary experiment has shown that the doubling time of cells is about 48 hours. Incidentally, the counting of cell population during the course is carried out by the classical exclusion method using Trypan Blue.

B. Cell sorting and endothelial cell purification

At the stage when the mixed cells have become confluent and a reasonable number of cells is obtained, endothelial cells are sorted out from among the mixed cells using FACS according to the following protocol. Thus, Dil-acetylated LDL (fluorescent dye marker; product of Biomedical Technologies) (briefly, Dil-Ac-LDL) is added to the mixed cell culture at a concentration of 1 μg/ml, followed by 24-hour incubation. This marker is taken up intracellularly through a scavenger pathway specific to endothelial cells and macrophages. After 24 hours, the cells are trypsinized to prepare a mixed cell suspension and sorting is performed using a cell sorter (FACS machine; product of Bectin Dickenson). According to the

size and emission of fluorescence, the cells are sorted into DiI-Ac-LDL-positive cells and DiI-Ac-LDL-negative cells. After the sorting, these types of cells are independently cultured and the culture is continued until $2x10^6$ endothelial cells are obtained.

C. Tissue construction

The first step of tissue construction comprises seeding cells in vitro. Specifically, a biodegradable culture matrix is seeded with about $1x10^6$ cells/cm^2 of DiI-Ac-LDL-negative fibroblasts.

Immediately following the seeding of a concentrated cell suspension on the matrix, the system is allowed to stand on the culture dish in a clean bench for 30-60 minutes, and thereafter about 50 ml of a culture medium is added. The culture medium is renewed every day as a rule and after 7 days, that is, one day before surgical transplantation, a further seeding is performed with a suspension of endothelial cells (about $2x10^6$ cells), whereby a monolayer of endothelial cells is obtained.

The above steps A-C show the cell isolation, culture and seeding procedures for the construction of a heart valve, a pericardium, or a blood vessel.

BEST MODE FOR CARRYING OUT THE INVENTION

The following examples are further illustrative of the present invention.

Example 1

· Construction of a vascular regeneration matrix

A glass test tube (10 mm in outside diameter) was wrapped around with a plain-weave cloth of poly-L-lactide fiber (photograph) in a double-cylindrical form. This assembly was set in a mold (12 mm in inside diameter) and a solution of L-lactide-caprolactone copolymer (50:50) in dioxane (5 %) was poured into the clearance, frozen and then lyophilized.

The cylindrical vascular prosthesis thus obtained was a cellular substrate reinforced with a fibrous material (Figs. 1 and 2).

· Cell culture

Through a small skin incision, a peripheral vein segment, about 5 mm long, was excised in a sterile environment and immediately immersed in the tissue culture medium. Cell isolation was carried out by the simple explant technique. As the cell culture medium, the standard cell culture medium DMEM mentioned above was used, and the medium was renewed every 2-3 days.

· Seeding of cells

The matrix prepared above was seeded with about $1x10^6$ cells/cm^2 of a mixed culture of endothelial cells and fibroblasts and the culture was continued for about 1 week until the matrix surface had been completely covered

with the cells.

· Animal experiment

The vascular prosthesis constructed as above was transplanted in the inferior vena cava of a young dog. As a result, no obliteration by rupture was found and a good patency could be verified angiographically at the 3rd postoperative month (the angiograph in Fig. 3). Thoracotomy at 6 months revealed regeneration of the autogenous blood vessel in agreement with the transplantation site.

In contrast, the matrix not reinforced with poly-L-lactide fiber ruptured in one week after substitution and the experimental animal succumbed to sudden death.

Claims

1. A matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material.

2. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1, wherein the bioabsorbable material is at least one member selected from the group consisting of polyglycolic acid, polylactic acid (D form, L form, DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymer, glycolic acid-caprolactone copolymer, lactic acid (D form, L form, DL form)-caprolactone copolymer and poly(p-dioxanone).

3. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating an artery, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

4. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating a vein, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polyglycolic acid.

5. The matrix for culturing cardiovascular

cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating a cardiac valve or a pericardium, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

6. The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1, wherein the sponge has a pore diameter of about 5 µm to about 100 µm.

7. A method for regenerating cardiovascular tissue comprising seeding cells on the matrix of Claim 1 and culturing the cells.

8. The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a blood vessel.

9. The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a cardiac valve.

10. The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a pericardium.

11. The method for regenerating cardiovascular tissue according to Claim 7, wherein the cells to be seeded are a mixed cell culture of two or three different kinds selected from the group consisting of endothelial

cells, smooth muscle cells and fibroblasts.

Abstract

Materials for culturing cardiovascular tissues wherein a sponge made of a bioabsorbable material is reinforced with a reinforcement made of a bioabsorbable material.

WO 01/17572
PCT/JP00/06129

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SAEGUSA, Eiji
Kitahama TNK Building
1-7-1, Doshomachi, Chuo-ku
Osaka-shi, Osaka 541-0045
JAPON

三枝特許事務所
01.3.26
弁理士 三枝英二

Date of mailing (day/month/year) 15 March 2001 (15.03.01)		
Applicant's or agent's file reference P00-34	**IMPORTANT NOTICE**	
International application No. PCT/JP00/06129	**International filing date** (day/month/year) 08 September 2000 (08.09.00)	**Priority date** (day/month/year) 09 September 1999 (09.09.99)
Applicant GUNZE LIMITED et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,
   FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,
   MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   15 March 2001 (15.03.01) under No. WO 01/17572

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/06129

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61L 27/48, 27/56, 27/58, C12N 5/06, 5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61L 27/00-27/60, 33/00-33/18, C12N 5/00-5/28, 11/00-11/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN), REGISTRY(STN), MEDLINE(STN), WPI(DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, 277678, A1 (Stichting Science Park Groningen), 10 August, 1988 (10.08.88), entire description, especially, Claims 1, 2, 6; Column 1; lines 1 to 4; the same column, line 45 to Column 2; line 52; examples 1 to 3, (Example I-III) & JP, 63-272355, A & AU, 8810376, A & NL, 8700113, E & NO, 8800193, A & DK, 8800209, A & FI, 8800147, A	1-6
Y	WO, 96/38188, A1 (Massachusetts Institute of Technology), 05 December, 1996 (05.12.96), entire description, especially, Claims 1, 3, 5; page 7; line 1 to page 8; line 24 & JP, 11-506364, A & US, 5766584, A & EP, 850073, A1 & AU, 9662928, A	1-6
Y	JP, 10-234844, A (Gunze Limited), 08 September, 1998 (08.09.98), entire description, especially, Claims 1, 2, 6; Column 2; lines 27 to 37; Column 3; lines 23 to 31; example 1 (Family: none)	1-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November, 2000 (15.11.00)	28 November, 2000 (28.11.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/06129

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, 734736, A1 (Toyo Boseki K.K.), 02 October, 1996 (02.10.96), entire description, especially, page 5; lines 38 to 44; example, (Examples) & JP, 8-266613, A & CA, 2173508, A & US, 5723010, A & US, 5876451, A	1-5
A	JP, 5-269196, A (Jinkou Kekkan Gijutsu Kenkyu Center K.K.), 19 October, 1993 (19.10.93), entire description (Family: none)	1-6
A	JP, 5-76588, A (Jinkou Kekkan Gijutsu Kenkyu Center K.K.), 30 March, 1993 (30.03.93), entire description (Family: none)	1-6
A	WO, 84/00302, A1 (Rijk-Suniversiteit te Groningen), 02 February, 1984 (02.02.84), entire description & JP, 59-501300, A & EP, 118458, A1 & NL, 8202893, A & AU, 8317100, A & NO, 8401008, A & BR, 8307439, A & BR, 8307440, A & FI, 8401050, A & DK, 8401067, A & US, 4661530, A & DE, 3374116, G	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/06129

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-11
because they relate to subject matter not required to be searched by this Authority, namely:

They pertain to methods for treatment of the human body by surgery or therapy.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2001 年3 月15 日 (15.03.2001)

PCT

(10) 国際公開番号
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(30) 優先権データ:
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(74) 代理人: 三枝英二, 外(SAEGUSA, Eiji et al.); 〒541-0045 大阪府大阪市中央区道修町1-7-1 北浜TNKビル Osaka (JP).

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

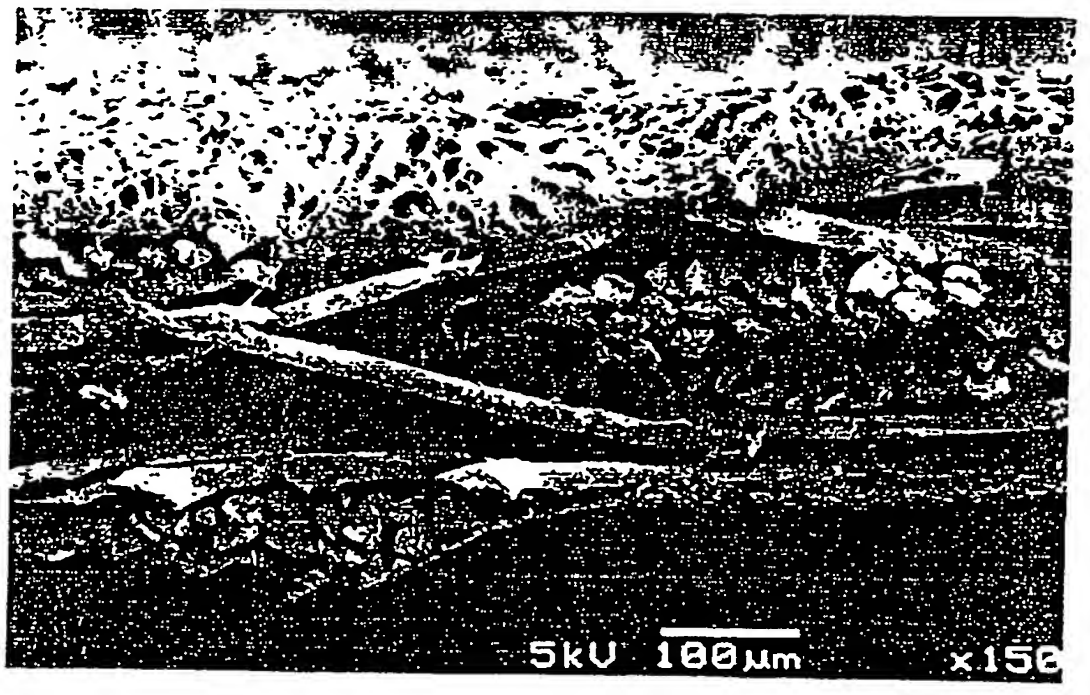
(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

[続葉有]

(54) Title: MATERIALS FOR CULTURING CARDIOVASCULAR TISSUES AND METHOD OF TISSUTE REGENERATION

(54) 発明の名称: 心血管系組織培養用基材および組織再生法



(57) Abstract: Materials for culturing cardiovascular tissues wherein a foamed matter made of a bioabsorbable material is reinforced with a reinforcing member made of a bioabsorbable material.

[続葉有]

WO 01/17572 A1

VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below:

That I am knowledgeable in the English language and in the language in which the below identified international application was filed, and that I believe the English translation of the international application No. PCT/JP00/06129 is a true and complete translation of the above identified international application as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Date

February 25, 2002

Full name of the translator Tomoko MAEDA

Signature of the translator Tomoko Maeda

Post Office Address Kitahama TNK Building 7-1, Dosho-machi
1-chome, Chuo-ku, Osaka-shi, Osaka 541-0045
Japan

PCT REQUEST

P00-34

Original (for **SUBMISSION**) - printed on 04.03.2002 12:10:27 PM

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form - PCT/RO/101 PCT Request**	
0-4-1	Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Japanese Patent Office (RO/JP)
0-7	**Applicant's or agent's file reference**	P00-34
I	**Title of invention**	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
II	**Applicant**	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	GUNZE LIMITED
II-5	Address:	1, Zeze, Aono-cho, Ayabe-shi, Kyoto 623-0011 Japan
II-6	State of nationality	JP
II-7	State of residence	JP
III-1	**Applicant and/or Inventor**	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	all designated States except US
III-1-4	Name	TOKYO WOMEN'S MEDICAL UNIVERSITY
III-1-5	Address:	8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-0054 Japan
III-1-6	State of nationality	JP
III-1-7	State of residence	JP

PCT REQUEST P00-34

Original (for **SUBMISSION**) - printed on 04.03.2002 12:10:27 PM

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	MORITA, Shinichiro
III-2-5	Address:	c/o Research & Development of GUNZE LIMITED 1, Ishiburo, Inokura Shinmachi, Ayabe-shi, Kyoto 623-0051 Japan
III-2-6	State of nationality	JP
III-2-7	State of residence	JP
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	SHIN'OKA, Toshiharu
III-3-5	Address:	c/o TOKYO WOMEN'S MEDICAL UNIVERSITY, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-0054 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	IMAI, Yasuharu
III-4-5	Address:	c/o TOKYO WOMEN'S MEDICAL UNIVERSITY, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-0054 Japan
III-4-6	State of nationality	JP
III-4-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	SAEGUSA, Eiji
IV-1-2	Address:	Kitahama TNK Building, 1-7-1, Doshomachi, Chuo-ku, Osaka-shi, Osaka 541-0045 Japan
IV-1-3	Telephone No.	06-6203-0941
IV-1-4	Facsimile No.	06-6222-1068
IV-1-5	e-mail	saegusa@po.sphere.ne.jp

PCT REQUEST P00-34

Original (for **SUBMISSION**) - printed on 04.03.2002 12:10:27 PM

IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	KAKEHI, Hiromichi; OHARA, Takeshi
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	09 September 1999 (09.09.1999)
VI-1-2	Number	1999-255803
VI-1-3	Country	JP

PCT REQUEST P00-34

Original (for **SUBMISSION**) - printed on 04.03.2002 12:10:27 PM

VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	**International Searching Authority Chosen**	Japanese Patent Office (JPO) (ISA/JP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	6	-
VIII-3	Claims	1	-
VIII-4	Abstract	1	p00-34.txt
VIII-5	Drawings	2	-
VIII-7	TOTAL	15	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-10	Copy of general power of attorney	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	Japanese	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	SAEGUSA, Eiji	Seal
IX-2	**Signature of applicant or agent**		
IX-2-1	Name (LAST, First)	KAKEHI, Hiromichi	Seal
IX-3	**Signature of applicant or agent**		
IX-3-1	Name (LAST, First)	OHARA, Takeshi	Seal

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/JP
10-6	**Transmittal of search copy delayed until search fee is paid**	

PCT REQUEST

P00-34

Original (for **SUBMISSION**) - printed on 04.03.2002 12:10:27 PM

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

SAEG108.001APC asg dea/koa

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,938	06/04/2002	Shinichiro Morita	SAEG108.001APC	4758

20995 7590 09/08/2004

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,938	MORITA ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/10&9/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims examined on the merits 1-11 which are all claims in the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (5,863,531) in view of Vyakarnam et al (6,534,084 B1) taken with Hinsch et al (EP 0 274 898) (listed on form 1449) and Japanese patent 3-23864 (listed on form 1449).

The claims are drawn to a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material. Also claimed is a method of culturing cardiovascular cells to regenerate cardiovascular tissue by seeding cells on the matrix and culturing the cells. The sponge has a pore diameter of about 5-100 μm.

Naughton et al disclose producing tissue *in vitro* by seeding cells on a three-dimensional structure having interstitial spaces which can be used to form tubular tissue structures (col 6, lines 55-60 and col 22, line 41) such as in the form of blood vessels (col 24, line 33), arteries (col 24, line 37) or veins (col 25, line 24). The three dimensional structure can be made of biodegradable material such as polyglycolic acid, polylactic acid or polyglycolic acid copolymer (col 9, lines 60-62). The three-dimensional structure can be made of a sponge (col 9, line 42).

Vyakarnam et al disclose foam structures that can be composed of copolymers of lactide such as a poly(L) lactide-co-E-caprolactone (col 6, line 45, col 9, lines 53-55 and col 12, lines 5-9), and which can be used to regenerate tissue such as tubular structures such as vascular grafts (col 3, lines 1 and 20-21, and col 9, lines 19-24). The pore size of the foam can be 30-50 μm or 100-200 μm (paragraph bridging cols 4 and 5). The foam can be reinforced with fibers (col 6, line 40).

Hinsch et al disclose a porous implant having a pore size of 10-200 µm for the growth of blood vessels in the form of a foam made of a resorbable polymer such as a copolymer of glycolide and lactide (page 4, lines 1-8). The foam may contain textile reinforcing elements such as fibers or knitted fabrics (page 3, lines 8-13).

The Japanese patent discloses a reinforced collagen sponge for implanting in tissue. The sponge is reinforced with fibers made of poly-L-lactic acid.

It would have been obvious to form the biodegradable polyglycolic acid copolymer tubular structures of Naughton et al with the biodegradable foam of Vyakarnam et al that is a copolymer of glycolide and lactide since this foam can be used for producing a tubular structure and has advantageous properties. It would have been further obvious to reinforce the foam with fibers as suggested by Hinsch et al and the Japanese patent using fibers to reinforce a foam implant. It would have been obvious to use fibers formed of poly-L-lactic acid as taught by the Japanese patent so thqt both the foam and fibers are bioabsorbable. Using polyglycolic acid as in claim 4 to form the fibers would have been a matter of obvious choice. A foam as disclosed by the references is a sponge. When forming the tubular structures of Naughton et al, cardiovascular cells are used and the tissue produced is cardiovascular tissue. The conditions of dependent claims would have been obvious from the disclosures of the references. Structures other than tubular structures such as a cardiac valve or pericardium as in certain dependent claims would have been obvious

from the many different structures disclosed by Naughton et al. Using two or more different cells as in claim 11 would have been obvious from Naughton et al using different types of cells together.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David M. Naff
Primary Examiner
Art Unit 1651

DMN
9/3/04

Notice of References Cited	Application/Control No. 10/070,938	Applicant(s)/Patent Under Reexamination MORITA ET AL.	
	Examiner David M. Naff	Art Unit 1651	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-5,863,531	01-1999	Naughton et al.	424/93.7
	B	US-6,534,084	03-2003	Vyakarnam et al.	424/443
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

FORM PTO-1449 U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SAEG108.001APC	APPLICATION NO. 10/070,938 PCT APPLICATION NO. PCT/JP00/06129
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (USE SEVERAL SHEETS IF NECESSARY)	APPLICANT Morita, et al.	
	FILED DATE: March 7, 2002 PCT FILING DATE: September 8, 2000	GROUP Unknown

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
		WO 84 84/00302	02/02/84	WIPO				
		EP 0 274 898	07/20/88	Europe				
		EP 0277 678	08/10/88	Europe				
		WO 96/08213	03/21/96	WIPO				
		EP 0 734 736	10/02/96	Europe				
		WO 96/38188	12/05/96	WIPO				
		WO 96/40175	12/19/96	WIPO				
		JP 63-255068	10/21/88	Japan			Abstract	
		JP 63-272355	11/09/88	Japan			Abstract	
		JP 1-230366	09/13/89	Japan			Abstract	
		JP 2-167156	06/27/90	Japan			Abstract	
		JP 3-23864	01/31/91	Japan			Abstract	
		JP 5-76588	03/30/93	Japan			Abstract	
		JP 5-269196	10/19/93	Japan			Abstract	
		JP 6-292716	10/21/94	Japan			Abstract	
		JP 10-234844	09/08/98	Japan			Abstract	

EXAMINER INITIAL	OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

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060502

EXAMINER	DATE CONSIDERED 9/3/04

*EXAMINER: INITIAL IF CITATION CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP 609, DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT

FORM PTO-1449 U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SAEG108.001APC	APPLICATION NO. 10/070,938
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (USE SEVERAL SHEETS IF NECESSARY)	APPLICANT Morita, et al.	
	FILING DATE June 4, 2002	GROUP 1623

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)
DM	1	4,725,273	02/16/88	Kazuaki Kira	623	1	
	2						
	3						
	4						
	5						
	6						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
DM	7	JP 62-44260	02/26/87	Japan			Abstract	
	8							
	9							
	10							
	11							
	12							

EXAMINER INITIAL		OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
DM	13	Shinoka, et al., "Creation of Viable Pulmonary Artery Autografts Through Tissue Engineering," The Journal of Thoracic and Cardiovascular Surgery, Vo. 115, No. 3, pp.536-545 March 1998
	14	
	15	
	16	
	17	

I:\DOCS\KOA\KOA-4292.DOC
091202

EXAMINER DM.	DATE CONSIDERED 9/3/04

*EXAMINER: INITIAL IF CITATION CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP 609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Please Direct All Correspondence to Customer Number **20995**

AMENDMENT / RESPONSE TRANSMITTAL

Applicant	:	Shinichiro Morita et al.
App. No	:	10/070,938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	NAFF, DAVID M.
Art Unit	:	4758

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

February 8, 2005
(Date)

Katsuhiro Arai, Reg. No. 43,315

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-identified application are the following enclosures:

(X) Amendment in 7 pages.

(X) A Supplemental Information Disclosure Statement and PTO/SB/08 equivalent listing 1 reference for consideration.

The fee has been calculated as shown below:

FEE CALCULATION				
FEE TYPE		**FEE CODE**	**CALCULATION**	**TOTAL**
Total Claims	14 - 20 = 0	1202 ($50)	0 x 50 =	$0
Independent Claims	1 - 3 = 0	1201 ($200)	0 x 200 =	$0
2 Month Extension		1252 ($450)		$450
Information Disclosure Statement				$180
			TOTAL FEE DUE	**$630**

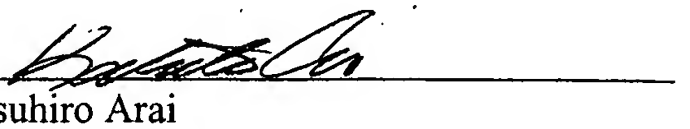
(X) An extension of time is hereby requested by payment of the appropriate fee indicated above.

(X) A check in the amount of $630 is enclosed.

Please Direct All Correspondence to Customer Number **20995**

(X) Return prepaid postcard.

(X) Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.



Katsuhiro Arai
Registration No. 43,315
Attorney of Record
Customer No. 20,995
(949) 760-0404

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020705

SAEG108.001APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Shinichiro Morita et al.
Appl. No.	:	10/070,938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	NAFF, DAVID M.
Group Art Unit	:	4758

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

February 8, 2005
(Date)

Katsuhiro Arai, Reg. No. 43,315

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed September 8, 2004, please reconsider the present application in light of the following amendments and comments.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

Please amend the Claim Form and Claim as follows. Insertions are shown underlined while deletions are ~~struck through~~.

1 (original): A matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material.

2 (original): The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1, wherein the bioabsorbable material is at least one member selected from the group consisting of polyglycolic acid, polylactic acid (D form, L form, DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymer, glycolic acid-caprolactone copolymer, lactic acid (D form, L form, DL form)-caprolactone copolymer and poly(p-dioxanone).

3 (original): The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating an artery, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

4 (original): The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating a vein, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polyglycolic acid.

5 (original): The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1 for use in regenerating a cardiac valve or a pericardium, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

6 (original): The matrix for culturing cardiovascular cells to regenerate cardiovascular tissue according to Claim 1, wherein the sponge has a pore diameter of about 5 μm to about 100 μm.

7 (original): A method for regenerating cardiovascular tissue comprising seeding cells on the matrix of Claim 1 and culturing the cells.

8 (original): The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a blood vessel.

9 (original): The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a cardiac valve.

10 (original): The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a pericardium.

11 (original): The method for regenerating cardiovascular tissue according to Claim 7, wherein the cells to be seeded are a mixed cell culture of two or three different kinds selected from the group consisting of endothelial cells, smooth muscle cells and fibroblasts.

12 (new): A vascular prosthesis comprising the matrix for culturing cardiovascular cells of Claim 1 which is seeded with a cell culture and cultured in vitro.

13 (new): The vascular prosthesis according to Claim 12, wherein the cell culture is a mixed cell culture of two or three different kinds selected from the group consisting of endothelial cells, smooth muscle cells and fibroblasts.

14 (new): The vascular prosthesis according to Claim 12, wherein the matrix surface is completely covered with the cells.

REMARKS

Claims 12-14 have been added. Support for these claims can be found throughout the specification, for example, page 12. No new matter has been added. Applicant respectfully requests entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejection Under 35 U.S.C. § 103

Claims 1-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Naughton et al in view of Vyakarnam et al taken with Hinsch et al and Japanese patent 3-23864. Applicant respectfully traverses the rejection.

The present invention is directed to, for example, a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material, and to a method for regenerating cardiovascular tissue comprising seeding cells on said matrix and culturing the cells.

The present invention achieves in at least an embodiment the remarkable effect of obtaining a matrix which allows cells to sufficiently adhere thereto, provides an optimum scaffold for cell proliferation, maintains satisfactory blood flow resistance in vivo till autogeneous tissue is regenerated, and is ultimately decomposed and absorbed in vivo.

Cited References

Naughton discloses stromal cell-based three-dimensional living stromal tissues that can be used as corrective structures in the body, including tubular structures that can be used to replace or repair blood vessels (column 6, lines 55 to 58). Naughton discloses examples of biodegradable matrices, such as of polyglycolic acid, in column 9, lines 59 to 63 in the specification. A collagen sponge is disclosed in column 9, line 42 in the specification. Naughton discloses that, in addition to fibroblasts and other stromal cells, smooth muscle cells, endothelial cells and the like can also be used (column 4, lines 23 to 30).

Vyakarnam discloses porous bioabsorbable polymer foams that have a gradient in composition and/or microstructure (column 1, lines 8 to 13, and column 4, lines 10 to 25). These foams are useful for regeneration of tissues such as vascular grafts (column 3, lines 13 to 23). Vyakarnam also discloses, in column 9, lines 53 to 56, bioabsorbable polymers such as

copolymers of lactide. In column 4, line 67 to column 5, line 2, Vyakarnam discloses foams with pore size of 30 μm to 50 μm and 100 μm to 200 μm in porous gradient.

Hinsch discloses a porous (average pore size of 10-200 μm) implant suitable for growing blood vessels, the implant being made of a resorbable polymer such as polylactide, in which at least one textile reinforcement made of resorbable plastic is embedded (abstract; page 2, lines 1 to 4 and 43 to 45; and page 3, lines 8 to 13).

JP3-23864 discloses a filler to be transplanted in vivo, the filler comprises a collagen sponge in which a fibrous bioabsorbable polymer (poly-L-lactic acid) is embedded therein (Abstract). This filler accelerates the growth of fibroblasts, maintains its shape and strength for a duration enough long for medical treatment, and is absorbed in vivo after treatment.

No Motivation to Combine Naughton/Vyakarnam with Hinsch/JP3-23864

The Examiner has asserted that it would have been obvious to form the biodegradable polyglycolic acid copolymer tubular structure of Naughton with the biodegradable foam of Vyakarnam, and it would have been further obvious to reinforce the foam with fibers as suggested by Hinsch and JP3-23864. However, the present invention is not obvious from the cited references for the reasons described below.

Naughton teaches a biodegradable matrix having a tubular structure that can be used to replace or repair a blood vessel. However, it does not disclose a reinforcement for reinforcing the biodegradable matrix.

Vyakarnam teaches a porous bioabsorbable polymer foam having a tubular structure used for regenerating blood vessels, etc., and harvesting the cells by seeding them onto the foams (column 18, from line 58). However, it does not disclose a reinforcement made of a biodegradable polymer.

The implant of Hinsch is made of a resorbable polyester such as polylactide or the like, is used for growing blood vessels, is porous having pores of which the average pore diameter is 10-200 μm, and has a textile reinforcement formed of resorbable plastic embedded therein. Hinsch is different from the present invention in that it does not teach that cells are grown by being seeded on the implant.

The filler disclosed in JP3-23864 uses poly-L-lactic acid. However, JP3-23864 is different from the present invention in that this filler is embedded in vivo as is, i.e., without

seeding and growing cells, and that the filler is not used for regenerating blood vessel or the like tissues.

Considering the above, both Naughton and Vyakarnam employ "tissue engineering" in which tissues are regenerated by seeding, culturing, and growing autogenous cells on a matrix, and the regenerated tissues are transplanted in vivo. However, Hinsch and JP3-23864 relate to implants used by simply embedding the implants in. vivo without seeding, culturing, growing the cells onto a matrix. Therefore, they are fundamentally different from Naughton and Vyakarnam.

In other words, Naughton and Vyakarnam, which disclose a method for regenerating tissues by employing tissue engineering, are totally different from Hinsch and JP3-23864, which do not employ tissue engineering, in terms of the techniques used, role and function thereof, etc. Therefore, there is no motivation in Naughton and Vyakarnam to combine the teachings thereof with those of Hinsch and JP3-23864. In other words, it would not have been obvious to arrive at employing "a reinforcement made of a biodegradable material" with "the foam formed of a biodegradable material" of Naughton and Vyakarnam.

None of the References Disclose the Subject Matter of Claims 3-5

The invention claimed in Claims 3-5 is directed to a matrix comprising a sponge and reinforcement suitable for the matrix to regenerate an artery, vein, heart valve, or pericardia (claims 3, 4 and 5). The present invention defines a sponge and reinforcement suitable for the regeneration of specific cardiovascular tissues. None of the cited references include such disclosures or teachings.

Naughton and Vyakarnam disclose a matrix for blood vessels (artery and vein) and like tubular structures. However, they neither teach nor suggest that such a matrix can be used for regeneration of a "heart valve" or "pericardia" as recited in claims 5, 9 and 10 of the present invention. Therefore, these claims are unobvious.

Furthermore, as described in Example 1 in the present specification, artificial blood vessels with and without a reinforcement exhibited significant differences in working-effects when implanted in the inferior vena cava of a young dog. Specifically, the matrix not reinforced with poly-L-lactide fiber ruptured one week after substitution and the dog suddenly died. In contrast, no obliteration by rupture was found in the matrix with a reinforcement of the present invention and revealed regeneration of the autogenous blood vessel in agreement with the

transplantation site. Even a skilled artisan would not have expected such a remarkable effect from the above-mentioned cited references.

For the reasons described above, Applicant respectfully submits that the present invention is not obvious from the cited references, and requests that the pending claims be allowed.

New Claims

Claims 12-14 have been added. These claims recite "seeded with a cell culture and cultured in vitro." As explained above, none of the references teaches or even suggests a reinforce matrix seeded and cultured in vitro. For example, Hinsch et al and JP3-23864 simply teach embedding implants in vivo. Thus, the references could not lead to the invention recited in Claims 12-14. It is respectfully submitted that these claims are allowable.

CONCLUSION

In light of the Applicant's amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Feb. 8, 2005

By: _____

Katsuhiro Arai
Registration No. 43,315
Attorney of Record
Customer No. 20,995
(949) 760-0404

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020805

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicant	:	Shinichiro Morita et al.
App. No	:	10/070,938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	NAFF, DAVID M.
Art Unit	:	4758

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

February 8, 2005
(Date)

Katsuhiro Arai, Reg. No. 43,315

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing in the above-identified application is a Supplemental Information Disclosure Statement by Applicant (PTO/SB/08 equivalent) listing 1 reference to be considered by the Examiner.

This Information Disclosure Statement is being filed before the mailing date of a final action and before the mailing of a Notice of Allowance. This Statement is accompanied by the fees set forth in 37 C.F.R. § 1.17(p). The Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Feb. 8, 2005

By: _____

Katsuhiro Arai
Registration No. 43,315
Attorney of Record
Customer No. 20,995
(949) 760-0404

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PTO/SB/08 Equivalent

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application No.	10/070,938
	Filing Date	June 4, 2002
	First Named Inventor	Shinichiro Morita et al.
	Art Unit	4758
(Multiple sheets used when necessary)	Examiner	NAFF, DAVID M.
SHEET 1 OF 1	Attorney Docket No.	SAEG108.001APC

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number *Number - Kind Code (if known)* Example: 1,234,567 B1	Publication Date MM-DD-YYYY	Name of Patentee or Applicant	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
		5,855,610	01-05-1999	Vacanti et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document *Country Code-Number-Kind Code* Example: JP 1234567 A1	Publication Date MM-DD-YYYY	Name of Patentee or Applicant	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T[1]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[1]

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020705

Examiner Signature	Date Considered

***Examiner:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

T[1] - Place a check mark in this area when an English language Translation is attached.

SAEG108.001APC asg
dea/kda/CPP

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,938	06/04/2002	Shinichiro Morita	SAEG108.001APC	4758

20995 7590 05/17/2005

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
NAFF, DAVID M

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,938	MORITA ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment of 2/11/05 in response to an office action of 9/8/04 added new claims 12-14.

Claims examined on the merits are 1-14, which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (5,863,531) in view of Vyakarnam et al (6,534,084 B1) taken with Hinsch et al (EP 0 274 898) and Japanese patent 3-23864 for reasons in the previous office action of 9/8/04, and for reasons herein.

The claims are drawn to a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue comprising a sponge made of a bioabsorbable material and a reinforcement made of a bioabsorbable material. Also claimed is a method of culturing cardiovascular cells to regenerate cardiovascular tissue by seeding cells on the matrix and culturing the cells. The sponge has a pore diameter of about 5-100 μm. The matrix can be in the form of a vascular prosthesis seeded with a cell culture and cultured *in vitro*. The cell culture can be a mixture of two or more different kinds of cells. The matrix surface of the prosthesis can be completely covered with cells.

Naughton et al disclose producing tissue *in vitro* by seeding cells on a three-dimensional structure having interstitial spaces

which can be used to form tubular tissue structures (col 6, lines 55-60 and col 22, line 41) such as in the form of blood vessels (col 24, line 33), arteries (col 24, line 37) or veins (col 25, line 24). The three dimensional structure can be made of biodegradable material such as polyglycolic acid, polylactic acid or polyglycolic acid copolymer (col 9, lines 60-62). The three-dimensional structure can be made of a sponge (col 9, line 42).

Vyakarnam et al disclose foam structures that can be composed of copolymers of lactide such as a poly(L) lactide-co-E-caprolactone (col 6, line 45, col 9, lines 53-55 and col 12, lines 5-9), and which can be used to regenerate tissue such as tubular structures such as vascular grafts (col 3, lines 1 and 20-21, and col 9, lines 19-24). The pore size of the foam can be 30-50 Tm or 100-200 Tm (paragraph bridging cols 4 and 5). The foam can be reinforced with fibers (col 6, line 40).

Hinsch et al disclose a porous implant having a pore size of 10-200 Tm for the growth of blood vessels in the form of a foam made of a resorbable polymer such as a copolymer of glycolide and lactide (page 4, lines 1-8). The foam may contain textile reinforcing elements such as fibers or knitted fabrics (page 3, lines 8-13).

The Japanese patent discloses a reinforced collagen sponge for implanting in tissue. The sponge is reinforced with fibers made of poly-L-lactic acid.

It would have been obvious to form the biodegradable polyglycolic acid copolymer tubular structures of Naughton et al with the biodegradable foam of Vyakarnam et al that is a copolymer of glycolide and lactide since this foam can be used for producing a tubular structure and has advantageous properties. It would have been further obvious to reinforce the foam with fibers as suggested by Hinsch et al and the Japanese patent using fibers to reinforce a foam implant. It would have been obvious to use fibers formed of poly-L-lactic acid as taught by the Japanese patent so thqt both the foam and fibers are bioabsorbable. Using polyglycolic acid as in claim 4 to form the fibers would have been a matter of obvious choice. A foam as disclosed by the references is a sponge. When forming the tubular structures of Naughton et al, cardiovascular cells are used and the tissue produced is cardiovascular tissue. The conditions of dependent claims would have been obvious from the disclosures of the references. Structures other than tubular structures such as a cardiac valve or pericardium as in certain dependent claims would have been obvious from the many different structures disclosed by Naughton et al. A vascular prosthesis as in claim 12 would have been obvious from Naughton et al disclosing a tubular structure in the form of blood vessels, arteries or veins. Using two or more different cells as in claims 11 and 12 would have been obvious from Naughton et al using different types of cells together. Cells completely covering the matrix as in claim 14 is inherent with producing a tubular structure as taught by Naughton et al.

Response to Arguments

Applicant's arguments filed 2/11/05 have been fully considered but they are not persuasive.

Applicants urge that Naughton et al and Vyakarnam et al are drawn to tissue engineering, and are totally different from Hinsch et al and the Japanese patent which do not employ tissue engineering, and there is no motivation to combine the teachings of Naughton et al and Vyakarnam et al with those of Hinsch et al and the Japanese patent. However, since the foam of Vyakarnam et al, which is used for tissue engineering can be reinforced with fibers, it would have been apparent that reinforcement is important irrespective of whether tissue is produced on the foam or sponge before implanting. Even after tissue is engineered on the foam or sponge, it is implanted and reinforcement would have been expected to be important for the same type of reasons as when tissue is not produced on the foam or sponge before implanting. Moreover, the invention of claims 1-6 does not require tissue to be present, and the matrix can be implanting without seeding with cells and culturing to produce tissue.

As to claims 3-5 that applicants urge are not disclosed by the references, Vyakarnam et al disclose foam structures composed of poly(L) lactide-co-E-caprolactone, and the Japanese patent discloses a sponge reinforced with fibers made of poly-L-lactic acid. It would have been well within the skill of the art to use the foam of Vyakarnam et al in Naughton et al and reinforce the foam with the fibers of the Japanese patent. The use of polyglycolic acid for

reinforcement as in claim 4 would have also be obvious since this polymer would have been expected to provide the same function as polylactic acid when used to make fibers.

The results in Example 1 are unpersuasive, since the references suggest using fibers to reinforce tubular structures to be implanted, and it would have been obvious to reinforce the vessel before implanting. The references would not have taught reinforcement if reinforcement had not needed to provide additional strength.

As to claims 12-14, Naughton et al, as well as Vyakarnam et al, suggest seeding and culturing on a matrix to be implanted. The references are combined together and must be considered as whole in combination rather than each alone.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 751-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David M. Naff
Primary Examiner
Art Unit 1651

DMN
5/16/05

Please Direct All Correspondence to Customer Number **20995**

AMENDMENT / RESPONSE TRANSMITTAL

Applicant	:	Shinichiro Morita et al.
App. No	:	10/070,938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	David M. Naff
Art Unit	:	1651

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

September 19, 2005
(Date)

C. Philip Poirier, Reg. No. 43,006

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-identified application are the following enclosures:

(X) Amendment in 6 pages with an English translation of the Morita Specificaton and Claims in 5 pages.

The fee has been calculated as shown below:

FEE CALCULATION				
FEE TYPE		**FEE CODE**	**CALCULATION**	**TOTAL**
Excess Claims > 20	10 - 20 = 0	1202 ($50)	0 x 50 =	$0
Independent > 3	1 - 3 = 0	1201 ($200)	0 x 200 =	$0
Multiple Claim	*1.16(j)*	1203 ($360)		$***
1 Month Extension	*1.17(a)(1)*	1251 ($120)		$120.00
2 Month Extension	*1.17(a)(2)*	1252 ($450)		$
3 Month Extension	*1.17(a)(3)*	1253 ($1,020)		$
			TOTAL FEE DUE	$120

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Shinichiro Morita et al.
Appl. No.	:	10/070,938
Filed	:	June 4, 2002
For	:	MATRIX FOR REGENERATING CARDIOVASCULAR TISSUE AND METHOD FOR REGENERATING CARDIOVASCULAR TISSUE
Examiner	:	David M. Naff
Group Art Unit	:	1651

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

September 19, 2005
(Date)

C. Philip Poirier, Reg. No. 43,006

AMENDMENT

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Final Office Action mailed May 17, 2005, please reconsider the present application in light of the following amendments and comments.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1-6. (Cancelled)

7. (Currently amended) A method for regenerating cardiovascular tissue comprising:

seeding cells on ~~the~~ a matrix ~~of Claim 1~~ comprising a sponge configured to regenerate cardiovascular tissue and made of a bioabsorbable material and a reinforcement made of a bioabsorbable material; ~~and~~

culturing the cells until the matrix surface is completely covered with the cells; and

embedding the matrix in vivo for regenerating cardiovascular tissue.

8. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a blood vessel.

9. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a cardiac valve.

10. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cardiovascular tissue to be regenerated is a pericardium.

11. (Original) The method for regenerating cardiovascular tissue according to Claim 7, wherein the cells to be seeded are a mixed cell culture of two or three different kinds selected from the group consisting of endothelial cells, smooth muscle cells and fibroblasts.

12-14. (Cancelled)

15. (New) The method for regenerating cardiovascular tissue according to Claim 7, wherein the bioabsorbable material is at least one member selected from the group consisting of polyglycolic acid, polylactic acid (D form, L form, or DL form), polycaprolactone, glycolic acid-lactic acid (D form, L form, DL form) copolymers, glycolic acid-caprolactone copolymers, lactic acid (D form, L form, DL form)-caprolactone copolymers and poly(p-dioxanone).

16. (New) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating an artery, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

17. (New) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating a vein, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polyglycolic acid.

18. (New) The method for regenerating cardiovascular tissue according to Claim 7 for use in regenerating a cardiac valve or a pericardium, wherein the sponge comprises a lactic acid-caprolactone copolymer and the reinforcement comprises polylactic acid.

19. (New) The method for regenerating cardiovascular tissue according to Claim 7, wherein the sponge has a pore diameter of about 5 μm to about 100 μm.

REMARKS

In the Office Action, the Examiner maintained the rejection of the pending claims as obvious under 35 U.S.C. § 103 over Naughton, et al. (U.S. Patent No. 5,863,531) in view of Vyakarnam, et al. (U.S. Patent No. 6,534,084) taken with Hinsch, et al. (EP 0 274 898) and Morita (Japanese Patent No. 3-23864).

By this amendment, Claims 1-6 and 12-14 have been cancelled. Claim 7 has been amended to more clearly define the present invention. Support for amended Claim 7 may be found at page 3, line 21 – page 4, line 7; page 6, lines 4-8; and Example 1. Furthermore, Claims 15-19 have been added. Support for new Claims 15-19 may be found at page 4, line 8 – page 5, line 11; page 6, line 9 - page 7, line 12; and in originally-filed Claims 2-6. No new matter has been added thereby. Thus, Claims 7-11 and 15-19 are currently pending in the application. The Examiner's rejections are traversed below.

Rejection under 35 U.S.C. § 103

The Examiner has maintained his previous rejection of all of the pending claims under 35 U.S.C. § 103(a) as being unpatentable over Naughton, et al. (U.S. Patent No. 5,863,531) in view of Vyakarnam, et al. (U.S. Patent No. 6,534,084) taken with Hinsch, et al. (EP 0 274 898) and Morita (Japanese Patent No. 3-23864). The Examiner has repeated the grounds for rejection from the first Office Action and has indicated that Vyakarnam's disclosure of a foam reinforced with fibers shows a motivation to combine Naughton and Vyakarnam with Hinsch and Morita.

The Examiner's rejection rests on two central propositions. First, the Examiner indicates that "the invention of claims 1-6 does not require tissue to be present, and the matrix can be implanting without seeding with cells and culturing to produce tissue." Office Action at 5. In response, Applicant has amended the claims to require that cells be seeded onto the matrix and completely cover it prior to embedding the matrix in vivo. Second, the Examiner concludes that one of skill in the art would have understood from the cited references that reinforcement would be important even if tissue were grown on the matrix before it was implanted. Specifically, the Examiner states that

> since the foam of Vyakarnam et al, which is used for tissue engineering can be reinforced with fibers, it would have been apparent that reinforcement is

> important irrespective of whether tissue is produced on the foam or sponge before implanting. Even after tissue is engineered on the foam or sponge, it is implanted and reinforcement would have been expected to be important for the same type of reasons as when tissue is not produced on the foam or sponge before an implanting.

Id.

With respect to this second proposition, Applicant respectfully submits that, upon closer consideration, the references cited by the Examiner teach away from the claimed combination. In brief, Vyakarnam discloses the use of reinforcing fibers only in foam used to regenerate bone or cartilaginous tissue attached to bone, where greater stiffness is required. Applicant submits that the Examiner has failed to show compatibility between bone or cartilaginous tissue and cardiovascular tissue. Vyakarnam's disclosure of tissue scaffoldings used in vascular repair does not include the use of reinforcing fibers. Naughton specifically criticizes the use of artificial reinforcing materials in blood vessels, where elasticity is required. Applicant respectfully submits that the Examiner has failed to consider this teaching-away disclosure. Neither Hinsch nor Morita contemplate tissue engineering in which cells are grown in the foam before implantation in the body, and therefore they only suggest that an open-cell foam having no natural tissue therein, which might be expected to be weaker than the surrounding tissue, should be reinforced with fibers before implantation. Applicant submits that one of ordinary skill in the art would not culture cells on the foam or sponge before implanting unless absolutely required to do so, because it is extremely burdensome to culture cells in this manner. Furthermore, Morita makes clear that the presence of such fibers is only required until the tissue is regenerated. Applicant notes that the tissue-covered matrix is reinforced in the pending claims. Considering the disclosure of the references as a whole, Applicant submits that one of skill in the art reading these references would be discouraged from placing reinforcing fibers in a matrix used for generating cardiovascular tissue via in vitro tissue culture followed by in vivo transplantation. The cited references at least provide no motivation for doing so. The results obtained in Example 1 were therefore surprising and non-obvious.

The disclosure of each reference will be discussed in detail below.

Vyakarnam '084

As the Examiner indicates, Vyakarnam discloses foam structures that can be composed of copolymers of lactide and which can be used to regenerate tissue such as vascular grafts. Furthermore, as the Examiner notes, Vyakarnam teaches that the foam may be reinforced with fibers. Specifically, the discussion of fibers to which the Examiner refers is within a section of the Vyakarnam specification discussing cartilage. Here, however, the reinforcing fibers are restricted to a section of the cartilage that attaches to bone, in which sufficient stiffness is required:

> [A]t the bottom of this structure there is a need for larger pores (about 150 μm to about 300 μm) with higher stiffness to be structurally compatible with cancellous bone. The foam in this section could be reinforced with ceramic particles or fibers made up of calcium phosphates and the like.

Vyakarnam '084 at col. 6, lines 36-41 (emphasis added). Furthermore, Vyakarnam also discusses the use of fibers in tissue scaffoldings for bone repair, which would clearly also require significant stiffness. Vyakarnam '084 at col. 8, lines 5-12. But although Vyakarnam specifically describes possible tissue scaffoldings for use in skin and vascular repair, the reference does not disclose the use of artificial reinforcing fibers in such applications. By inference, Vyakarnam suggests to one of skill in the art that the use of reinforcing fibers is only preferable where higher stiffness is required, such as in those parts of cartilage which are connected to bone or in bone itself.

This understanding of Vyakarnam is reinforced by the discussion of Hinsch '898 therein. Vyakarnam discusses Hinsch in the "Background of the Invention" section, specifically noting that Hinsch teaches the reinforcement, with fibers or the like, of a porous open cell foam. Vyakarnam '084 at col. 1, lines 36-41. However, Vyakarnam then specifically criticizes Hinsch as deficient. Vyakarnam '084 at col. 1, lines 48-49.

Naughton '531

As the Examiner indicates, Naughton discloses foam structures that may be used in regenerating vasculature. However, Naughton does not teach the use of fibrous reinforcing materials such as those of the present application. In fact, Naughton specifically criticizes the use in the prior art of artificial materials to provide "the strength and elasticity required of blood vessels in vivo," and notes that the criticized prior art technique resulted in a construction that

"completely lacked elastin." Naughton '531 at col. 4, lines 2-6. The presence of elastin "gives arteries the ability to stretch with every contraction of the heart." Naughton '531 at col. 24, lines 48-50. Naughton therefore indicates that when natural components such as elastin are present in tubular biological replacement tissues grown on an unreinforced matrix, they may be used as replacement tissues in the body:

> The different biological structures described below have several features in common. They are all tubular structures primarily composed of layers of stromal tissue with an interior lining of epithelium (gastrointestinal and genitourinary) or endothelium (blood vessels). Their connective tissues also contain layers of smooth muscle with varying degrees of elastic fibers, both of which are especially prominent in arterial blood vessels. By including and sustaining these components in three-dimensional cultures according to the present invention, the tissues they compose can attain the special structural and functional properties they require for proper physiological functioning in vivo. They can then serve as replacements for damaged or diseased tubular tissues in a living body.

Naughton '531 at col. 22, lines 49-62. Naughton would accordingly suggest two things to one of skill in the art. One is that the replacement tissues grown on the disclosed unreinforced matrices or foams have sufficient strength to be implanted in the body as prosthetic cardiovascular tissue once the tissue culture is complete. The other is that it is not advisable to employ artificial reinforcing materials to supply the strength and elasticity necessary for blood vessels in vivo, as this may hinder the development of the cellular and extracellular components required for the regenerated blood vessels to properly function.

Hinsch '898

Hinsch discloses an implant made of a resorbable polyester such as polylactide or the like that has pores with an average pore diameter of 10-200 μm and has a textile reinforcement formed of resorbable plastic embedded therein. Hinsch does not teach or suggest that cells may be grown by being seeded on the implant prior to implantion. Rather, the Hinsch implant is designed to be implanted and then colonized by the surrounding tissue. In other words, Hinsch describes the problem solved by the invention as the need for an implant "which, despite the adequately open-cell structure to permit the growing-in of cells and blood vessels, ha[s] an adequate strength and particularly tensile strength." Hinsch '898 at p. 2, lines 51-53 (emphasis added). Hinsch does not suggest that cells can be seeded on the implant ex vivo. Accordingly,

one of skill in the art would understand from Hinsch that reinforcement of an open-cell foam implant may be necessary when cells are not seeded onto the implant prior to implantation in vivo.

Morita '864

An English-language translation of the Morita specification and claims is attached. As the Examiner notes, Morita discloses a filler material for use in vivo that uses poly-L-lactic acid. Like Hinsch, Morita does not disclose seeding and growing cells on the filler material prior to implantation. Neither does Morita disclose that the filler material is used for regenerating blood vessels or similar cardiovascular tissue structures.

Furthermore, Morita clearly indicates that reinforcement is not necessary when fully regenerated tissue is present. Specifically, the implant disclosed in Morita is said to "maintain[] its strength and shape over a long period of time until the regeneration of the tissue." Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). One of skill in the art would accordingly understand from Morita that if tissue was generated ex vivo by tissue engineering techniques, artificial reinforcement of the implant would not be necessary.

Applicant submits that the combined teachings of these references would counsel one of skill in the art to avoid the use of artificial reinforcements in cardiovascular tissue engineered ex vivo. Vyakarnam's awareness of the possibility of using reinforcing fibers, and his choice to employ such fibers only where greater stiffness is required (as opposed to the elasticity required of blood vessels), together with Naughton's criticism of the use of artificial reinforcements in blood vessel prostheses, would indicate to one of skill in the art that use of reinforcing fibers was at best unnecessary, and probably unwise, as it might make the resulting prostheses too stiff or hinder the development of the natural components that provide elasticity. Both Hinsch and Morita indicate that the purpose of reinforcing fibers is simply to provide the mechanical strength which is lacking in an uncultured open-cell structure which is implanted into the body. *See* Hinsch '898 at page 2, lines 51-53 and page 3, lines 8-11; Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). Indeed, Morita suggests that the fibers are only required when the tissue is not yet fully regenerated. Thus, these disclosures support the view that the reinforcing fibers are only necessary in a matrix for culturing cardiovascular tissue when the

matrix has not yet been cultured with cells, and that when such cells are present on the matrix, they would provide sufficient strength for the prosthetic tissue in vivo.

In view of these combined teachings, as described above, Applicant submits that one of skill in the art would have concluded that it was inadvisable, and at least unnecessary, to place artificial reinforcing fibers into a matrix seeded with cardiovascular cells to regenerate a blood vessel before implantation, as the presence of the fibers could make the prosthesis too stiff or impede the development of the cardiovascular tissue. Accordingly, the results obtained by the present invention, as shown in Example 1, are surprising and the invention is not obvious over the combination of cited references.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 19, 2005

By: C. Philip Poirier

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MORITA ET AL., JP 3-23864

Specification

1. Title of the Invention

Filler material for living tissue

2. Claims

1. A filler material for living tissue, characterized in comprising a composite material of collagen sponge and a bioabsorbable polymer material.

2. A filler material for living tissue in accordance with Claim 1, characterized in that a fibrous bioabsorbable polymer material is mixed into or embedded in the collagen sponge.

3. A filler material for living tissue in accordance with Claim 1 or Claim 2, characterized in that the bioabsorbable polymer material is poly-L-lactic acid.

3. Detailed Description of the Invention

(Industrial Applicability)

The present invention relates to a filler material which may be employed in the surgical treatment of wounds and defects and the like or in orthopedic surgery.

(Background Art)

In the surgical treatment of wounds or defects or the like, and in orthopedic surgery, filler material is embedded in damaged areas in order to regenerate tissue and to prevent contracture.

It is required of such materials that they have little reactivity with tissue, that they promote the proliferation of fibroblasts, and that they maintain their strength and shape over a long period of time until the tissue is regenerated. Furthermore, it is a particularly required property that such materials maintain their shape in order to prevent contracture of the tissue

during actual use, and additionally, that they rapidly disappear from within the body and do not remain as a foreign object after the regeneration of the tissue.

Microporous collagen sponges have been proposed for such purposes; however, they do not have the above properties.

(Problem to be Solved by the Invention)

That is to say, collagen sponges in which, for example, glutaraldehyde is cross-linked do not maintain the requisite long-term shape and strength required for use in treatment, and within two to three months of three implantation in the body, they are completely broken down and absorbed by the body and disappear.

The present invention solves the defects present in the prior art; it provides a novel filler material having little reactivity with tissue and which promotes the propagation of fibroblasts, maintains its shape and strength over a long period of time, and furthermore is absorbed into the body after treatment.

(Means for Solving the Problem)

Moreover, the present invention is characterized in that it comprises a composite material consisting of collagen sponge and a biodegradable polymer material, fibrous poly-L-lactic acid is employed as the biodegradable polymer material, and this material is mixed into or embedded in the collagen sponge.

(Function)

By combining poly-L-lactic acid, which is slow to degrade within the body, with the collagen sponge, the present invention makes it possible to maintain the structural pores of the sponge over a long period of time, and furthermore, to promote the propagation of fibroblasts in

the interior of the material by means of the combination with fibrous poly-L-lactic acid, and also to maintain the strength and shape over the long period of time required for treatment.

Hereinbelow, the composition will be described.

(Embodiment)

0.3 g of 3-Denier poly-L-lactic acid fibers (molecular weight 80,000) were twined in a sliver, and placed in a vessel having length, width, and height dimensions of 6 x 2 x 2 cm, and this was agitated for a period of 60 minutes at 1,800 rpm with 50 g of a 0.3% hydrochloric acid solution of porcine atherocollagen. Next, this was freeze-dried for a period of 48 hours and sterilized in alcohol to produce the filler material of the present invention.

The filler material obtained in this manner had the appearance of a composite in which poly-L-lactic acid fibers were randomly embedded in a microporous sponge structure.

Furthermore, as shown in Table 1, in comparison with the prior art sponge composed only of collagen, the rupture strength, rupture ductility, and Young's modulus of the present invention are considerably higher, and it represents a dramatic improvement. Furthermore, the pore size is larger.

The comparative example in the Table is a sponge comprising only collagen that was prepared by a method identical to that described above using 50 g of a 0.2% hydrochloric acid solution of porcine atherocollagen, using glutaraldehyde as a crosslinking agent.

Table 1

	Strength	Ductility	Young's Modulus	Pore Size
Present invention	7.7	132	27.8	97
Comparative Example	1.3	40	8.0	63

These values were obtained by the JIS methods. Furthermore, the units are as given below.

Strength: rupture strength (x 10^5) (dyne/cm^2)

Ductility: rupture ductility (%)

Young's Modulus: (x 10^5) (dyne/cm^2)

Pore Size: (μm)

The filler material of the present invention obtained by the method described above was employed in animal testing using the following methods, and the histology, strength, and state of contracture thereof were assessed.

(Applied Example)

A 2 x 2 cm section of the back muscle of a 350 g Wistar rat was removed, and an approximately 2 cm section of the filler material of the present invention was implanted at this spot, and the progress thereof was observed.

(After One Month)

The infiltration of fibroblasts into the peripheral portions of the sponge was confirmed, but the cells had not infiltrated into the central portion thereof.

(After Three Months)

The cellular infiltration into the central section of the sponge was increased in comparison with after two months.

(After Six Months)

In portions of the central part of the sponge, the fibroblasts were arranged in a single direction.

Histologic studies revealed that fibroblasts had sufficiently penetrated the central part of the sponge three to four months after implantation, and the tissue was completely regenerated after six months.

The state of contracture was assessed using a method in which the volume was measured by means of plaster modeling. Using the comparative example above, only approximately 5-15% of the initial volume remained after two months, and after four months, the absorption into the body was complete, and the material had disappeared. In contrast, using the filler material of the present invention, 35-50% of the original volume was present, even after six months, and this represents a striking difference.

(Effects of the Invention)

As is clear from the effects obtained when the filler material of the present invention was applied, as described above, the material has the required properties for use and does not react with tissue, promotes the propagation of fibroblasts, maintains its strength and shape over a long period of time until the regeneration of the tissue, functions to prevent contracture of the tissue, and is broken down and absorbed into the body after the regeneration of tissue, so that the material has all the properties necessary for use, and may be effectively employed.

The proportions in which the collagen sponge and the bioabsorbable polymeric material are combined, as well as the size of the poly-L-lactic acid fibers and the like may be appropriately selected in accordance with the required properties.

As described above, the present invention provides a biodegradable filler material having a novel composition which was not conventionally available.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,938	06/04/2002	Shinichiro Morita	SAEG108.001APC	4758

20995 7590 10/12/2005

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EXAMINER
NAFF, DAVID M

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/070,938	Applicant(s) MORITA ET AL.	
	Examiner David M. Naff	Art Unit 1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *7-11 and 15-19*.

   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

David M. Naff
Primary Examiner
Art Unit: 1651

Continuation of 11. does NOT place the application in condition for allowance because: of the following reasons. Applicants state that the claims have been amended to require seeding the matrix with cells and culturing until the matrix is completely covered with the cells before embedding the matrix in vivo. However, as set in the rejection, Naughton et al disclose seeding a matrix with cells and producing in vitro tissue such as a tubular tissue structure, and implanting the tissue structure. In producing such a tissue structure, the matrix will be completely covered with cells or otherwise the structure not be formed.

Applicants urge that Vyakarnam et al use reinforcing fibers only in foam when regenerating bone or cartilaginous tissue. However, cardiovascular tissue can contain cartilaginous tissue. Furthermore, Vyakarnam et al disclose producing a scaffold for vascular repair, and recognize (col 1, lines 38-45) that it is known to use foam reinforced with fibers for repair of blood vessels (Hinsch et al ('898). It would have been obvious when Hinsch et al is also considered to reinforce a scaffold used to produce tissue structures in the form of blood vessels or arteries as taught by Naughton et al. While Vyakarnam et al may consider Hinsch et al to be deficient in certain aspects, this is not related to the use of reinforcing fibers, but because the foam of Hinsch et al lacks the anisotropic features of natural tissues. In fact, Vyakarnam et al state that the Hinsch foams had an advantage of having regular pore sizes and shapes that could be controlled by the processing conditions, solvents selected, and the additives (col 1, lines 40-45).

Applicants urge that Naughton et al criticizes the use of artificial reinforcing material in blood vessels. However, the invention as broadly claimed in claims 7-11 and 19 does not require a reinforcing material that is artificial. The bioabsorbable material of claims 7-11 and 19 can be connective tissue proteins that serve as a support as disclosed by Naughton et al. As to the other claims that require the reinforcement to comprise polylactic acid or polyglycolic acid, such reinforcement would have been obvious when Hinsch et al and the Japanese patent are considered which teach reinforcement with fibers that can be made of polylactic acid. The use of synthetic polymer fibers for reinforcement is clearly obvious as an alternative to extracellular matrix protein such as elastin and collagen produced by cells that provide support in the matrix of Naughton et al. Naughton et al is not applied alone, but in combination with other references, and the references must be considered together as a whole rather than each alone. It would have been well within the ordinary skill of the art to select between two alternatives of providing support to a foam matrix. While Hinsch et al and the Japanese patent may not seed the foam with cells before implanting, seeding with cells is suggested by Naughton et al, as well as Vyakarnam et al (paragraph bridging cols 18 and 19), to provide a matrix containing tissue or cells in vitro prior to implanting. It is granted that the Japanese patent discloses that the scaffold (filler material) breaks down and is absorbed into the body after tissue is formed. However, the matrix of the present claims is bioabsorbable and will break down and be absorbed into the body when tissue is regenerated in vivo after implanting.

Contrary to applicants' assertion, there is no suggestion by the references that using artificial reinforcing fibers in a matrix seeded with cardiovascular cells will make the matrix too stiff or impede the development of the cardiovascular tissue. If too great a stiffness occurred, Vyakarnam et al, Hinsch et al and the Japanese patent would not have disclosed providing support for a sponge or foam to be implanted with synthetic polymer fibers. If the fibers impeded the development of tissue, the references would not have used the reinforcing fibers since the matrix of the references serves as a support for cells to form tissue even when the matrix is implanted without seeding with cells in vitro. After implanting, cells infiltrate the scaffold and form tissue in vivo. .

(e)

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(54) **Implant.**

(57) The invention relates to an implant from an open-cell, foam-like plastic material based on resorbable polyesters, such as poly-p-dioxanone, other polyhydroxycarboxylic acids, polylactides or polyglycolides, as well as their copolymers, in which one or more textile reinforcing elements made from resorbable plastic are embedded in an open-cell plastic matrix with a pore size of 10 to 200 µm.

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IMPLANT

The invention relates to porous implants of open-cell, foam-like plastic materials based on resorbable polyesters such as poly-p-dioxanones, polylactides or polyglycolides and their copolymers, as well as to a process for producing the same by the freeze drying of a solution of polymers at low temperatures and under a high vacuum.

Of late, body-resorbable implants have been used in medicine, which offer a temporary support for damaged, injured or missing body parts and which are replaced by the body's own structures to the extent in which they are resorbed. Implants made from compact materials are unsuitable due to the excessive rigidity of the materials and also and in particular because the implants cannot be penetrated by body fluids, cells and blood vessels, so that no new tissue can form.

The textile structure according to US patent 3 739 773 produced from fibres or monofilaments of resorbable plastic, is, as a flat structure, too permeable for body fluids and therefore is unsuitable for many purposes, e.g. for replacing the dura.

In addition, porous, resorbable prostheses are known from DE-OS 32 18 150, DE-OS 33 34 595 and US patent 4 292 972. Apart from pourable ceramic materials, such as e.g. hydroxyl apatite, they relate to biopolymers such as hydrocolloids, gelatins or collagen, as well as synthetic resorbable polymers. However, up to now no product in the latter category has achieved practical significance. Products formed from peptide-containing polymers are unsuitable, because they cause strong foreign body reactions up to repulsion and excapsulation.

As a result of their good physiological compatibility synthetic resorbable polymers, e.g. of aliphatic hydroxycarboxylic acids have been proposed for porous implants, e.g. according to US patent 4 181 983, according to which lactides are polymerized with a catalyst such as tetraphenyl tin, whilst excluding oxygen, at elevated temperatures of 150 to 200°C and in vacuo. Following reprecipitation from dioxan/water in benzene, the polymer obtained is dissolved in a solvent mixture of 30% methanol and 70% benzene and mixed with a surfactant, such as sodium oleate. The polylactide concentration in the final benzene solution is preferably 3.5% by weight and the quantity of the sodium oleate used as the wetting agent is in the range 0.25 to 2.5% by weight. The benzene solution is then frozen in dry ice and freeze dried under high vacuum for 18 hours. However, these products suffer from the disadvantage that through the high molecular weight (M_w) of the polylactides of over 100 000 the resorption process takes too long and the pore sizes of under 20 µm obtained are unsuitable, because no body fluids penetrate the pores, no cells migrate in and no blood vessels can grow in, so that no new tissue can form. The necessary addition of detergents can only facilitate the penetration of liquids, but cannot aid the following physiological healing processes. Moreover, surface-active compounds, such as synthetic, anionic, cationic or amphoteric surfactants or soap, which improve the absorbtion of tissue fluids in the foam materials, are not physiologically unobjectionable.

Other conventional processes for producing porous, open-cell, foam-like materials with chemically acting blowing agents are unsuitable, because blowing agent residues are left behind in the foam or reactive products are formed, which can at least partly decompose sensitive polymers, such as resorbable polyesters.

High pressure gassing processes, in which the plastic in solid or pasty form is gassed in a heated mould with a blowing gas mixture and then compressed, prefoamed by pressure reduction following the end of the gelling process and then the foam block obtained is again heated and inflated in a stabilizing furnace are unsuitable, because to obtain a uniform pore size it is necessary to add surface-active compounds and/or nucleating agents, which remain in the foam and are unusable for medical implants.

The problem of the present invention is to propose porous implants and a process for the production thereof, whereby the pores have a suitable size for the growth of blood vessels and cells, namely an average diameter of 10 to 200 and preferably 20 to 150µm, because excessively small pores with a diameter of under 10 µm cannot grow through and large pores lead to a deterioration in the mechanical stability of the porous implants.

According to the invention, it must be possible to produce such open-cell polymers without the use of the adjuvants conventionally employed for foam production, such as surface-active substances, stabilizers, lubricants, physical or chemical blowing agents.

It is finally a problem of the invention to propose implants which, despite the adequately open-cell structure to permit the growing in of cells and blood vessels, have an adequate strength and in particular tensile strength.

Thus, for solving the problem of the invention, an implant of the aforementioned type is proposed, which is constructed in accordance with the characterizing part of the main claim, preferred embodiments

being given in the subclaims. In addition, for solving the inventive problem, processes for producing the implants are proposed.

The invention is based on the surprising finding that the tensile strength of such implants is dependent on the polymer content of the solution to be freeze dried and is only dependent to a reduced extent on the production conditions adopted during freeze drying, such as the freezing rate. However, a part is also played by the choice of solvent and this also influences the pore size distribution, the pore size and the pore shape.

It has surprisingly been found that on incorporating textile reinforcing elements of resorbable plastic such as fibres, yarns, braids, knitted fabrics and the like, it is possible to significantly improve the mechanical strength, without modifying the porosity characteristics, flexibility and elasticity of the foam materials. As a function of the choice of reinforcing elements, the mechanical strength can be increased in one or more directions in space, in that e.g. parallel fibres or threads increase the stability in only one direction and net-like flat structures improve the same in all directions of the corresponding surfaces.

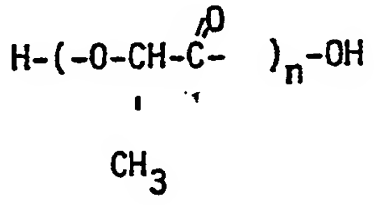
The invention is further illustrated hereinafter by means of examples.

I.Production of the Plastic Matrix

The production of the starting polymers is described hereinafter:

Example A: Polylactides

The starting polymer is produced in that purified lactide crystals are polymerized with 0.002% by weight of tetraphenyl tin, whilst excluding oxygen, for 4 hours in a temperature range of 150 to 200°C, the polymer obtained is precipitated from dioxan by adding water and then dried under a high vacuum. These polylactides have the following general formula:

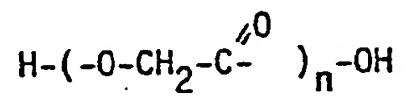


in which n has a value of 300 to 1200 corresponding to a molecular weight of 20 000 to 85 000.

Poly-L-lactide, poly-DL-lactide, as well as copolymers of these two substances and copolymers with glycolides can in particular be used for the inventive products and processes. Apart from glycolides, the polylactides can also contain other monomers, such as are referred to e.g. in US patent 4 181 983, column 3, lines 26 to 36.

Example B: Polyglycolides

The inventively used polyglycolides are obtained by the polymerization of glycolic acid and have the following general formula:



in which n is such that the molecular weight is in a range 10 000 to 500 000. These polyglycolides are prepared in that glycolide is polymerized with tin (II)-octanoate and glycolic acid, whilst excluding oxygen and in vacuo, for approximately 4 to 5 hours at 185 to 230°C and after cooling the polyglycolide is isolated as a white, opaque, viscous material. The inherent viscosity, measured in 1,1,1,3,3,3-hexafluoro-2-propanol is in the range 0.5 to 4.

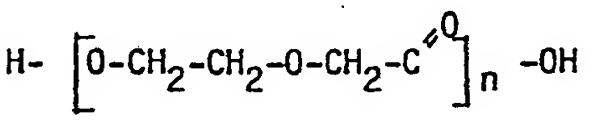
Example C: Copolymers of Glycolide and Lactide

9 parts by weight of glycolide and 1 part by weight of L-lactide are polymerized with glycolic acid and tin (III)-caprylate, as described in DE-OS 21 62 900, whilst excluding oxygen and moisture for approximately 4 hours at 200°C. The inherent viscosity of the polymer is 0.5 to 2.5 when measured in 1,1,1,3,3,3-hexafluoro-2-propanol.

Block copolymers of glycolide and lactide can also be used for the inventive products and processes, as described in DE-OS 28 49 785.

Example D: Polydioxanone

The inventively used polydioxanone has the following general formula



Polydioxanone is polymerized by the ring-opening polymerization of 2-oxo-1,4-dioxan in the presence of Sn catalists, such as e.g. tin (II)-caprylate at 120 to 150°C, whilst excluding oxygen and moisture, within 1 to 4 hours. The inherent viscosity (measured in 1,1,1,3,3,3-hexafluoro-2-propanol) of the polymer is in the range 0.5 to 3 and preferably 1.5 to 2.2.

II. Preparation of the Plastic Solution or Dispersion

Decisive for the preparation of the plastic matrix are the solvent chosen and the concentration of the resorbable plastic in the solvent to be freeze dried and optionally, in the case of a modified process, the addition of crystalline additives. Other solvents can be used, particularly in the latter case.

A. Solvent influence

According to the invention use is made of the following solvents:

a) 1,4-dioxan

b) 1,4-dioxan with an acetate of a C_2 to C_5 alcohol, namely ethyl acetate in the ratio 9:1,

c) hexafluoroisopropanol and as the comparison solvent

d) benzene with and without surfactant.

In each case 5 g of a poly-L-lactide according to example A are introduced into 100 g of the particular solvent and frozen from 20°C to -60°C in between 30 and 300 seconds and then freeze dried in vacuo.

The following table I shows the influence of the solvent selection on the pore structure of the polymer matrix.

TABLE I

Influence of the Solvent Selection on the Pore Structure

	Solvent	Pore Characterization
A-a	dioxan	open, round pores ; diameter 20-50 µm
A-b	dioxan/ethylacetate 9:1	open, round pores ; diameter 20-60 µm
A-c	hexafluoroisopropanol	open, round pores, fibrous ; diameter 10-50 µm
$A\text{-}d_1$	benzene	long channels with a diameter under 10 µm, a few oval pores of 20 - 100 µm
$A\text{-}d_2$	benzene + 2.5% surfactant	elongated pores (fibrous product); diameter 5-25 µm

The values of table I clearly show that only the inventively used solvents lead to a suitable polymer matrix. Similar results were obtained with the other polymerizable polymers according to example B (polyglycolides), example C (copolymers) and example D (polydioxan), as is shown by table II.

B. Influence of the Concentration

Different polymers in different concentrations were treated in a solvent mixture of dioxan and ethyl acetate in a ratio of 9:1 as in A-b) and freeze dried. The following table III shows that excellent pore sizes and distributions are obtained on respecting a concentration in the middle of the inventive concentration range.

TABLE II

Influence of the Solvent Selection on the Pore Structure of Copolymers of L-Lactide and Glycolide

Glycolide	Lactide	Solvent	Pore Characterization
(Weight Ratio in the Copolymer)			
90	10	HFIP	Fibrous, round, open pores, diameter approximately 20 - 100µm
30	70	dioxan/ethylacetate 9:1	Round, open pores with a diameter of 20 - 50 µm

TABLE III

Influence of the Polymer Concentration on the Pore Size

Polymer	Concentration (g/100 ml solvent)	Pore Characterization		
Poly-L-lactide	5	open, round pores;	diameter	20- 50µm
	7.5	open, round pores;	diameter	20-100µm
	12	open, round pores;	80% of the pores 20% of the pores ≤	20-100µm 20µm
	16	open, round pores;	10% of the pores 90% of the pores ≤	20- 30µm 20µm
Copolymer of glycolide and lactide 3:7	12	open, round to elongated pores;	80% of the pores 20% of the pores <	20-100µm 20 or > 100µm
Copolymer of glycolide and lactide 3:7	7.5	open, round to elongated pores;	diameter	20- 80µm
Poly-D,L-lactide	7.5	open, round pores;	88% of the pores 10% of the pores ≤ 2% of the pores	20-100µm 20µm 100-150µm

C. Adjusting the Pore Size Distribution by Crystalline Additives

4 parts of a copolymer of L-lactide and glycolide (9:1) and 1 part of citric acid are pulverized, screened and classified, the mixture being dissolved and/or suspended with 40 parts of 1,1,1,3,3,3-hexafluoro-2-propanol. As described in A, this mixture is frozen and freeze dried.

The citric acid is extracted with tetrahydrofuran from the resulting crude foam.

The foam contains circular, open pores, whose pores sizes are largely dependent on the particle size distribution of the citric acid used. An example is given in table IV.

TABLE IV

Influence of Crystalline Additives on the Pore Structure

Particle Size	Citric Acid	Pore Size in Foam	
80%	20µm to 40µm	75%	70µm to 40µm
80%	⩽ 20µm	90%	⩽ 20µm

III. Production of the Implants

Example 1

Different solutions of 2.0 to 30.0 g of poly-L-lactide are in each case dissolved in 100 ml of 1,4-dioxan/ethylacetate (90:10). A reinforcing element of the copolymer of L-lactide and glycolide in the weight ratio of 9:1 is in each case introduced into these solutions. The net in a dish is then frozen for 30 to 90 seconds to -60°C and then freeze dried.

Table V shows the value of the tensile strength of the polymer matrix without reinforcing inserts, determined with a tensiometer at 50 mm/min and a 2x10x50 mm test piece, the tensile strength through the surface of fracture gave the indicated tensile strength.

The tests revealed a rise in the tensile strength of the polymer matrix with increasing polymer concentration (no. 1-4) and under lower freezing conditions (test 5), as well as the comparatively inferior values in the case of a conventional solvent (tests 2 and 6 compared with test 7).

TABLE V

Tensile Strength of Porous Implants Without Reinforcing Elements

Test No.	Polymer Concentration (g/100ml of solvent)	Tensile Strength N/mm^2	Freezing Conditions	Solvent
1	4	0.10	A	1,4-dioxan/ethyl acetate 9:1
2	6	0.35	A	
3	10	0.90	A	
4	15	1.95	A	
5	4	0.28	B	
6	6	0.53	A	1,4-dioxan/ isoamyl acetate 19:1
7	6	0.30	A	benzene

A $20^{o}C$ to $-60^{o}C$ in 30-300 seconds

B $20^{o}C$ to $-130^{o}C$ in 30-300 seconds

Table VI shows the surprising increase in the tensile strength when using textile reinforcing elements in a polymer matrix according to example 1.

TABLE VI

Tensile Strength of Reinforced Porous Implants

Polymer Concentration (g/100ml of solvent)	Tensile Strength N/mm^2	Reinforcing Element
4	0.10	without
4	1.35	2dpf yarn, length 2-5 cm
4	8.0	knitted net
10	1.30	2dpf yarn, 1-5 mm
10	10.2	knitted net

Table VII shows the increase in the tensile strength of porous tubular implants with woven reinforcing elements of different weaving structures.

TABLE VII

Breaking Force of Porous Implants with Woven Reinforcing Elements

Breaking Force	Reinforcing Element
1.4N	none
40	thick-walled hose, 2x56 denier threads
70	impervious hose, 4x56 denier threads
150	very thick-walled, impervious hose, 8x56 denier threads

Test pieces:	external diameter 4 mm internal diameter 2.7 mm
Polymer concentration:	5g/100ml of solvent
Reinforcing element:	copolymer of L-lactide and glycolide 1:9

Claims

1. Implant of an open-cell, foam-like plastic material based on resorbable polyesters such as poly-p-dioxanone, other polyhydroxy carboxylic acids, polylactides or polyglycolides, as well as their copolymers, characterized in that one or more reinforcing elements of a textile nature formed from resorbable plastic are embedded in an open-cell plastic matrix with a pore size of 10 to 200 µm.

2. Implant according to claim 1, characterized in that compared with the resorbable plastic of the matrix, the resorbable plastics of the textile reinforcing elements have the same or a slower resorbability.

3. Implant according to claim 1, characterized in that the textile reinforcing elements are knitted, woven, twisted, braided or as felts in the form of fibres, threads, hoses, strips or fleeces.

4. Implant according to claims 1 to 4, characterized in that the open-cell plastic matrix has a pore size of 20 to 150 µm.

5. Implant according to claims 1 to 3, characterized in that the density of the plastic matrix is 0.05 to 0.60 g/cm^3.

6. Process for the production of an implant according to claims 1 to 5, characterized in that poly-p-dioxanone, polylactides or polyglycolides are dissolved in a solvent in a concentration of 5 to 30 parts by weight of polymer and the textile reinforcing element is frozen in a mould together with the plastic solution and then the solvent is removed by freeze drying.

7. Process according to claim 6, characterized in that the solvent used is hexafluoroisopropanol, 1,4-dioxan or a mixture of 1,4-dioxan and an acetate of a C_2 to C_5 alcohol in a volume ratio of 99:1 to 50:50.

8. Process according to claims 6 and 7, characterized in that use is made of poly-p-dioxanone with an inherent viscosity of 0.5 to 3.0 or polylactides with an inherent viscosity of 0.5 to 2.2 or polyglycolides with an inherent viscosity of 0.5 to 4.0.

9. Modification of the process according to claims 6 to 8, characterized in that the textile reinforcing element is impregnated with the plastic solution and then frozen and freeze dried.

10. Modification of the process according to claims 6 to 8, characterized in that crystalline organic compounds, salts of organic acids or inorganic salts are added to the solvents and after freeze drying are extracted from the implant with a suitable inert solvent.

L1 ANSWER 2 OF 3 WPINDEX (C) 2002 THOMSON DERWENT
AN 1991-077288 [11] WPINDEX
DNN N1991-059719 DNC C1991-032836
TI Filler for biological tissue which promotes fibroblast growth - consists of collagen sponge and a biodegradable, absorbable high mol.wt. material e.g. poly-L-lactic acid.
DC A96 D22 P34
PA (GUNZ) GUNTER & ZIMMERMANN CONSTR DIV
CYC 1
PI JP 03023864 A 19910131 (199111) * <--
JP 2805086 B2 19980930 (199844) 3p A61L027-00
ADT JP 03023864 A JP 1989-159307 19890620; JP 2805086 B2 JP 1989-159307 19890620
FDT JP 2805086 B2 Previous Publ. JP 03023864
PRAI JP 1989-159307 19890620
IC A61L027-00
ICM A61L027-00
AB JP 03023864 A UPAB: 19930928
A new filler for biological tissues consists of a cpd. material comprising collagen sponge and a biodegradable-and-absorbable high molecular material. In a pref. application a fibrous biodegradable-and-absorbable material is mixed or embedded in the sponge.
The high molecular material is pref. poly-L-lactic acid.
USE/ADVANTAGE - The filler undergoes no tissue responses, promotes the growth of fibroblasts, retains strength and shape until thorough recovery of tissues, prevents the contracture of tissues, and disappears through biodegradation and absorption after the recovery. In an example, the filler was prepd. by twining poly-L-lactic acid thread of mol. wt. 80,000 into a sliver, pouring a 0.3% HCl soln. of pig-originated atherocollagen while stirring at 1800 rpm for 1 hr., drying by freezing for 48 hrs., and sterilising with alcohol. @(0/0pp) ng
FS CPI GMPI
FA AB
MC CPI: A03-C01; A09-A; A12-S04; A12-V03A; D09-C

⑲日本国特許庁(JP)　⑪特許出願公開

⑫公開特許公報(A)　平3−23864

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A 61 L 27/00　U　6971−4C

審査請求　未請求　請求項の数 3　(全3頁)

⑤4発明の名称　生体組織用充填材

⑳特　願　平1−159307

㉒出　願　平1(1989)6月20日

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明　細　書

1．発明の名称

生体組織用充填材

2．特許請求の範囲

1．コラーゲンスポンジと生体分解吸収性高分子材料との複合材料より成ることを特徴とする生体組織用充填材。

2．繊維状の生体分解吸収性高分子材料がコラコラーゲンスポンジ中に混在し、もしくは埋入されて成ることを特徴とする請求項(1)項記載の生体組織用充填材。

3．生体分解吸収性高分子材料がポリ−L−乳酸であることを特徴とする請求項(1)、(2)項記載の生体組織用充填材。

3．発明の詳細な説明

(産業上の利用分野)

本発明は、損傷、欠損等の外科的治療、整形外科手術等に使用される充填材に関する。

(従来技術)

損傷、欠損等の外科的治療、及び、整形外科手術等においては組織の再生、拘縮を防止する目的において、欠損部に充填材が埋入される。

かかる素材としては、組織反応が少なく、線維芽細胞の増殖を促し、組織が再生するまで長期にわたってその強度、形状が維持される機能が求められる。また、特に適用中においては組織の拘縮を防止する目的において保形性を有する機能が求められ、また、組織の再生後においては異物として体内に残留することなく速やかに消失することが理想とされる。

かかる目的に対し、ミクロポーラスなコラーゲンスポンジが提案されているが、上記の機能を満足しない。

(発明が解決しようとする問題点)

即ち、例えば、グルタールアルデヒドを用いて架橋させたコラーゲンスポンジは、生体に埋入後2〜3ヶ月後には完全に生体に分解吸収されて消失してしまい治癒に必要な長期の強度、保形性を維持しない。

本発明は、かかる従来の欠点を解消し、組織反

応が少なく、且つ、線維芽細胞の増殖を促すと共に、長期にわたって形状、強度が維持され、また治癒後は生体に吸収される新規な充填材を提供したものである。

（問題を解決するための手段）

しかるに、本発明はコラーゲンスポンジと生体分解吸収性高分子材料との複合材料より成り、かかる生体分解吸収性高分子材料として繊維状のポリーＬ－乳酸を用いたこと、およびこれをコラーゲンスポンジ中に混在、もしくは埋入させて構成したことに特徴を有するものである。

（作用）

本発明は、コラーゲンスポンジ中に生体内での分解速度の遅いポリーＬ－乳酸を混在させて複合化させたことによってスポンジ構造のｐｏｒｅを長期にわたって維持でき、また、繊維状のポリーＬ－乳酸との複合化によって内部への線維芽細胞の増殖を促すと共に、治癒に必要な長期にわたっての強度、形状の維持を可能としたものである。

以下、その構成について、例示する。

（構成例）

３デニールのポリーＬ－乳酸糸（分子量80000）０．３ｇをからめてスライバー状とし、これを縦、横、深さが夫々６×２×２ｃｍの容器に入れ、これに豚由来のアテロコラーゲン０．３％塩酸溶液５０ｇを１８００ｒｐｍにて６０分間撹拌して注いだ。次いで、これを４８時間凍結乾燥し、アルコールにて滅菌して本発明充填材を構成した。

このようにして得た充填材は、ミクロポーラスなスポンジ構造の間にポリーＬ－乳酸糸がランダムに埋入されて複合化された外観を呈した。

また、その物性値は第１表に示すように従来のコラーゲン単独のスポンジと比較し、破断強度、破断伸度、ヤング率が格段に高い値を示し、著しい改善が成された。また、PoreSizeも大きくなっている。

尚、表における比較例は架橋剤としてグルタールアルデヒドを使用した豚由来のアテロコラーゲン０．２％塩酸溶液５０ｇを前記と同様の方法によって処理して得たコラーゲン単独のスポンジである。

第１表

	強　度	伸　度	ヤング率	PoreSize
本発明	7.7	132	27.8	97
比較例	1.3	40	8.0	63

尚、これの測定はＪＩＳ法に準じた。また、その単位は以下の通りである。

強度：破断強度（×10^6）、(dyne/cm²)

伸度：破断伸度（％）

ヤング率：（×10^6）、(dyne/cm²)

PoreSize：(μm)

上記の方法により得た本発明充填材を以下の方法により動物実験に供し、組織学的検討と内部の状態を観察した。

（適用例）

体重３５０ｇのウィスター系ラットの背部筋層上を２×２ｃｍ大に剥離し、その部分に約２ｃｍ＊大の本発明充填材を埋植し、経過を観察した。

＜１ヶ月後＞

スポンジ内周部分で線維芽細胞の侵入が認められるが中央部では細胞未侵入。

＜３ヶ月後＞

スポンジ中央部への細胞侵入は２ヶ月後に比べて増加している。

＜６ヶ月後＞

スポンジ中央部へ線維芽細胞が一定の方向で並ぶ部分ができた。

組織学的検討において埋植３～４ヶ月後にスポンジの中央部まで線維芽細胞が十分に侵入し、６ヶ月後においては完全に組織が構築された。

一方、内部の状態については石膏模型により、その容積を測定する方法によって行なったが、上記比較例によるものは２ヶ月後で初期体積の５～１５％しか残存せず、４ヶ月後では殆ど生体内に吸収され、消失するという結果であったが、本発明充填材によると６ヶ月後においても初期体積の３５～５０％が残存し、かかる面においても顕著

な差が見られた。

（発明の効果）

以上のように本発明による充填材は、その実用結果からも明らかなように、用途上の要求特性である、組織反応がないこと、線維芽細胞の増殖を促すこと、組織が再生するまで長期にわたってその強度、形状が維持されること、組織の拘縮を防止する機能を有すこと、組織の再生後は体内に分解吸収されて消失してしまうこと等、この種の用途に必要な機能を全て兼ね備えたものであり、効果的な適用が可能なものである。

尚、コラーゲンスポンジと生体分解吸収性高分子材料との複合化比率、およびポリーＬ－乳酸繊維の繊度等はその用途、必要機能等に応じて任意に選択可能なものである。

以上のように本発明は、従来にない新規な構成の生体組織用充填材を提供したものである。

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MORITA ET AL., JP 3-23864

Specification

1. Title of the Invention

Filler material for living tissue

2. Claims

1. A filler material for living tissue, characterized in comprising a composite material of collagen sponge and a bioabsorbable polymer material.

2. A filler material for living tissue in accordance with Claim 1, characterized in that a fibrous bioabsorbable polymer material is mixed into or embedded in the collagen sponge.

3. A filler material for living tissue in accordance with Claim 1 or Claim 2, characterized in that the bioabsorbable polymer material is poly-L-lactic acid.

3. Detailed Description of the Invention

(Industrial Applicability)

The present invention relates to a filler material which may be employed in the surgical treatment of wounds and defects and the like or in orthopedic surgery.

(Background Art)

In the surgical treatment of wounds or defects or the like, and in orthopedic surgery, filler material is embedded in damaged areas in order to regenerate tissue and to prevent contracture.

It is required of such materials that they have little reactivity with tissue, that they promote the proliferation of fibroblasts, and that they maintain their strength and shape over a long period of time until the tissue is regenerated. Furthermore, it is a particularly required property that such materials maintain their shape in order to prevent contracture of the tissue

during actual use, and additionally, that they rapidly disappear from within the body and do not remain as a foreign object after the regeneration of the tissue.

Microporous collagen sponges have been proposed for such purposes; however, they do not have the above properties.

(Problem to be Solved by the Invention)

That is to say, collagen sponges in which, for example, glutaraldehyde is cross-linked do not maintain the requisite long-term shape and strength required for use in treatment, and within two to three months of three implantation in the body, they are completely broken down and absorbed by the body and disappear.

The present invention solves the defects present in the prior art; it provides a novel filler material having little reactivity with tissue and which promotes the propagation of fibroblasts, maintains its shape and strength over a long period of time, and furthermore is absorbed into the body after treatment.

(Means for Solving the Problem)

Moreover, the present invention is characterized in that it comprises a composite material consisting of collagen sponge and a biodegradable polymer material, fibrous poly-L-lactic acid is employed as the biodegradable polymer material, and this material is mixed into or embedded in the collagen sponge.

(Function)

By combining poly-L-lactic acid, which is slow to degrade within the body, with the collagen sponge, the present invention makes it possible to maintain the structural pores of the sponge over a long period of time, and furthermore, to promote the propagation of fibroblasts in

the interior of the material by means of the combination with fibrous poly-L-lactic acid, and also to maintain the strength and shape over the long period of time required for treatment.

Hereinbelow, the composition will be described.

(Embodiment)

0.3 g of 3-Denier poly-L-lactic acid fibers (molecular weight 80,000) were twined in a sliver, and placed in a vessel having length, width, and height dimensions of 6 x 2 x 2 cm, and this was agitated for a period of 60 minutes at 1,800 rpm with 50 g of a 0.3% hydrochloric acid solution of porcine atherocollagen. Next, this was freeze-dried for a period of 48 hours and sterilized in alcohol to produce the filler material of the present invention.

The filler material obtained in this manner had the appearance of a composite in which poly-L-lactic acid fibers were randomly embedded in a microporous sponge structure.

Furthermore, as shown in Table 1, in comparison with the prior art sponge composed only of collagen, the rupture strength, rupture ductility, and Young's modulus of the present invention are considerably higher, and it represents a dramatic improvement. Furthermore, the pore size is larger.

The comparative example in the Table is a sponge comprising only collagen that was prepared by a method identical to that described above using 50 g of a 0.2% hydrochloric acid solution of porcine atherocollagen, using glutaraldehyde as a crosslinking agent.

Table 1

	Strength	Ductility	Young's Modulus	Pore Size
Present invention	7.7	132	27.8	97
Comparative Example	1.3	40	8.0	63

These values were obtained by the JIS methods. Furthermore, the units are as given below.

Strength: rupture strength (x 10^5) (dyne/cm^2)

Ductility: rupture ductility (%)

Young's Modulus: (x 10^5) (dyne/cm^2)

Pore Size: (μm)

The filler material of the present invention obtained by the method described above was employed in animal testing using the following methods, and the histology, strength, and state of contracture thereof were assessed.

(Applied Example)

A 2 x 2 cm section of the back muscle of a 350 g Wistar rat was removed, and an approximately 2 cm section of the filler material of the present invention was implanted at this spot, and the progress thereof was observed.

(After One Month)

The infiltration of fibroblasts into the peripheral portions of the sponge was confirmed, but the cells had not infiltrated into the central portion thereof.

(After Three Months)

The cellular infiltration into the central section of the sponge was increased in comparison with after two months.

(After Six Months)

In portions of the central part of the sponge, the fibroblasts were arranged in a single direction.

Histologic studies revealed that fibroblasts had sufficiently penetrated the central part of the sponge three to four months after implantation, and the tissue was completely regenerated after six months.

The state of contracture was assessed using a method in which the volume was measured by means of plaster modeling. Using the comparative example above, only approximately 5-15% of the initial volume remained after two months, and after four months, the absorption into the body was complete, and the material had disappeared. In contrast, using the filler material of the present invention, 35-50% of the original volume was present, even after six months, and this represents a striking difference.

(Effects of the Invention)

As is clear from the effects obtained when the filler material of the present invention was applied, as described above, the material has the required properties for use and does not react with tissue, promotes the propagation of fibroblasts, maintains its strength and shape over a long period of time until the regeneration of the tissue, functions to prevent contracture of the tissue, and is broken down and absorbed into the body after the regeneration of tissue, so that the material has all the properties necessary for use, and may be effectively employed.

The proportions in which the collagen sponge and the bioabsorbable polymeric material are combined, as well as the size of the poly-L-lactic acid fibers and the like may be appropriately selected in accordance with the required properties.

As described above, the present invention provides a biodegradable filler material having a novel composition which was not conventionally available.

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